The Effect of Clopidogrel on CRP Levels in Subjects with CAD: A Prospective Randomized Trial

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A. Study Purpose anal Rational

An individual living in today's world is more likely to die from coronary artery disease (CAD) than from any other cause. Recent advances in the study of CAD have deterniined that inflarnmation of the coronary arteries plays an important role in both the development of coronary blockages and the disruption of those blockages that cause heart attacks. C-reactive protein (CRP) is a protein in the blood whose levels increase during times of inflammation, and levels of CRP have been shown to predict who is more likely to develop complications of CAD.

There has been recent interest in investigating whether some of the drugs that are currently used to treat CAD have an effect on the level of inflarru-nation, and by extension CRP, in the body. Both statins, a group of.'cholesterol lowering drugs, and abc1ximab, a drug used to prevent blood clots in coronary arteries during stenting (a procedure designed to open up clogged arteries), have been shown to lower levels of CRP. Clopidour, a drug, that prevents coronary clots in a way similar to aspirin, has recently been shown to be of benefit for pallents that are having mild heart attacks or severe angina (chest pair). Whether clopidogrel lowers levels of CRP in those in whom it is elevated not known. The present study is designed to address this question.

B. Study Desiqn and Statistical Analysis

Potential subjects will be screened with CRP assays, and only those subjects with elevated levels of CRP will be enrolled. Study subjects will be randomized to receive either clopidogrel or matching placebo for 8 weeks. For each subject, a computer will generate a random number from 1-100. For those subjects with a number from 1-50, study drug A will be given. For those with a number from 51-100, study drug B will be given. The identity of drugs A and B (clopidogrel or placebo) will be known only to the central dispensing pharmacy. During the study, subjects will be allowed to continue to receive the drugs that normally take for their condition. However, subjects already receiving clopidogrel will not be eligible (see below). CRP levels will be measured at the end of the study period and compared to those at baseline. At the end of the study period, subjects will resume their previous drug regimens at the discretion of their physicians.

The distribution of CRP levels in the population is not bell-shaped. Standard parametric analysis cannot, therefore be used. The distribution of the change in CRP levels in response to other drugs that have been studied is bell shaped, however. For this reason, the mean change in CRP levels at the end of the study period versus baseline will be calculated, and potential significance of the difference in these means will be compared with Student's unpaired t test. Based on the 15% difference in CRP levels seen in previous studies and the standard deviation of the distribution ofthese changes, the number of patients needed In order to have an 80% power to detect this change with a $p < 0.05$ indicating, significance is estimated to be 307 in each arm. Means or proportions for baseline clinical characteristics will be computed for subjects in each arm of the study, and the significance of any differences in the means will be tested with Student's unpaired t test; difterences in proportions will be tested with the χ^2 statistic.

C. Study Procedure

The sole procedure required of the study will be the drawing of approximately 5ml of whole blood and study outset and at 8 weeks. Blood is normally drawn from this population of patients in the

course of their standard treatment 1-2 times a year. Subjects may feel minor discomfort from the needle used to draw blood. Subjects will also be required to come to safety and adherence visits at week 4 of the study.

D. Study Drugs (see package insert)

Clopidogrel is approved by the FDA for use in patients with peripheral arterial disease, unstable coronary disease, prior heart attacks, and prior strokes. It is given as a onetime dose ot-300mg by rriouth for the first day, followed by 75mg per day thereafter. It should not be used in patients who are allergic to it or who have an active problern with bleeding (such as an ulcer).

The major side effect of clopidogrel is bleeding. In a study that compared aspirin with clopidogrel, patients that received clopidogrel had a rate of gastrointestinal hemorrhage of' 2.7% and of intracranial hemorrhage of 0.4%. The corresponding rates for aspirin were 2.7% and 0.5% differences not considered significant. In a study that compared aspirin alone with aspirin plus clopidogrel, over the course of 12 months, subjects receiving both drugs had a in statistically significant increase in major bleeding versus subjects receiving only aspirin (3.7% vs. 2.7%). There was no difference in the rates of intracranial and fatal bleeds between the two groups.

Ticlopidine, a drug similar to clopidogrel, has been associated with a rare (0.8% incidence) reduction in the numbers of neutrophils in the blood (cells that help fight infection), a potentially serious condition. Clopidogrel appears to be much safer in this regard, although this complication was reported in one patent out of the 9599 that received the drug in a recent trial.

Other less serious reactions to the drug include GI upset, rash, and flu-like symptorns.

Safety of the study drugs and adherence to the dosage regimen will be followed by office visits at week 4 of the study where subjects will be interviewed about adverse reactions and pills will be counted. Subjects with serious adverse reactions, as judged by a safety-ı nonitoring panel, will be withdrawn.

E. Medical Devices

Not applicable

F. Study Questionnaires

Subjects will be administered a questionnaire on enrollment into Oe trial. The questionnaire will ask about the subject's personal identifiers, age, sex, CAD risk factors, current use ofdifferent medications used to treat CAD, and the presence of conditions that might disallow administration of the study drug or make interpretation of the results of the trial difficult.

G. Study Subjects

Subjects will be included for study if they are 21-75yrs, have had an Ml (as defined as a troponin level greater than or equal to 2.0) at least 8 weeks prior to enrollment with stable disease since the event, and have no evidence of congestive heart failure clinically with an ejection fraction greater than or equal to 25% on TTE (if avallable). Subjects will be excluded from the study of they have had an intracranial hemorrhage or endoscopically confirmed peptic ulcer in the last year or intra-abdominal surgery in the last 8 weeks, are taking oral anti-coagulation therapy, have a history of rheumatoid arthritis, temporal arteritis, osteomyelitis, SLE, chronic infection, active cancer, bleeding diathesis, renal insufficiency (CrCl < 50) or have a projected life span less than the study period. Subjects with an allergy to clopidogrel and those taking clopidogrel at any point within the 8 weeks prior to screening would be excluded as well. Subjects with CRP levels at baseline greater than or equal to 0.66 mg/dL as measured by a high sensitivity assay manufactured by Dade Behring would subsequently be randomized.

The recruitment of minority populations and of women would be encouraged.

H. Recruitment of Subjects

Subjects would be recruited for the study with use of flyers posted around the medical center, as well as from direct referral from private physicians. On initial contact with potential subject, eligibility based on clinical inclusion/exchision criteriawill be established. Infori-ned consent will be solicited, and the subject's baseline blood levels will be drawn. Only those subjects, with eligible CRP levels will be randomized.

I. Confidentiality of Study Data

Data on study subjects would be kept in a secure location; with subject files solely identified using a consecutive number system. A master key, correlating subject ideritifier numbers with personal data would be kept in a secure, central location.

J. Potential Conflict of Interest

The investigators will not materially profit in any way from the study results.

K. Location of Study

Blood samples will be drawn in the outpatient unit of the GCRC. Laboratory Measurements will be carried out in the GCRC Core Lab.

L. Potential Risks

The main risk to study subjects is of bleeding, as outlined above and in the attached package insert. Data available in a large population of people indicate that there is a 1 % absolute increase in the risk of serious bleeding over the course ofa year of treatment. The risk associated with 8 weeks or administration would be siginficantly attenuated. The subject may additionally experience a mild amount of discomfort or bruising related to blood drawing. Potential adverse outcomes will be monitored as above.

M. Potential Benefits

Subjects will likely not derive clinical benefit from a. short course of clopidogrcl, should they be randomized to this arm. Subjects in the placebo arm will not benefit. However, the results ofthe study should help shed light on the way in which the drugs we use to treat CAD, guide future therapies, and benefit society as a whole.

N. Alternative Therapies

Not applicable.

O. Compensation to Subjects

Subjects will not be monetarily compensated for their participation.

P. Costs to Subjects

Subjects will not incur costs beyond those of standard care in participation in tile study.

Q. Minors as Research Subjects

Not applicable.

R. Radiation or Radioactive Substances

Not applicable.

S. References

1. Liuzzo, *et. al.* The prognostic value of CRP and serum arnyloid A protein in severe unstable angina. New England Journal of Medicine. 331(7) 417-424, 1994.

2. The CARPIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin ill patients at risk of ischaemic events (CAPRIE). Lancet 348 1329-1339; 1996.

3. Ridker, *et. al.* Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. New England Journal Of Medicine. 336(14) 973-979; 1997.

4. Ridker, *et. al.* Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with averalge cholesterol levels. Circulation 98(9) 839-844: 1998.

5. Ridker, *et. al.* Long-term effects of pravastatin on plasina concentration Of CRP. Circulation 100(3) 230-123.45-, 1999.

6. Ridker, *et. al.* Rapid reduction in CRP with cerivestatin among 785 patients with primary hypercholesterolemia. Circulation 103(9) 1191-119.3; 2001.

7. Jialall, *et. al.* Effect of hydroxymethyl glutaryl coenzyme A redUCtaSC inhibitot therapy oil high sensitive CRP levels. Circulation 103(15) 1933-1935; 2001.

8. Lincoff, *et. al.* Abciximab suppresses the rise in levels of circulation inflammatory markers after percutaneous coronary revascularization. Circulation 104(2) 163-167; 2001.

9. Rlidker, *et. al.* Measurement of CRP for the targeting of statin therapy in the primary prevention of' acute coronary syndromes. New England Journal of Medicine 344(26) 1959-1965: 2001.

10. Feldman *et. al.* Effects of low dose aspirin on serum CRP and thromboxane B_2,_concentrations; A placebo--controlled study using a highly sensitive CRP assay. Journal of the American College of Cardiology. 37(8) 2037-2040.

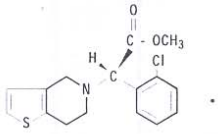
11. The CURE Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. New England Journal of Medicine. 345(7) 494-502, 2001.

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 insolube 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 hydrogenated castor oil, hydroxypropylcellulose, mannitol, microcrystalline cellulose and polyethylene glycol 6000 as inactive ingredients. The pink film coating contains ferric oxide, hydroxypropyl methylcellulose 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 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 (≈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 two double-blind trials: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of PLAVIX to aspirin, and the CURE study (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), a comparison of PLAVIX to placebo, both given in combination with aspirin and other standard therapy.

The CAPRIE trial was a 19,185-patient, 304-center, international, randomized, double-blind, parallel-group study comparing PLAVIX (75 mg daily) to aspirin (325 mg daily). The patients randomized had: 1) recent histories of myocardial infarction (within 35 days); 2) recent histories of ischemic stroke (within 6 months) with at least a week of residual neurological signs; or 3) 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.

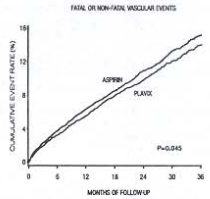
Table 1: Outcome Events in the CAPRIE Primary Analysis

	PLAVIX 9599		aspirin 9586	
Patients				
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 the 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 athrorothrombotic 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.

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 a 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

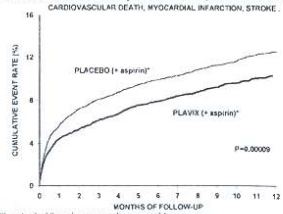
Outcome	PLAVIX (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)	Relative Risk Reduction (%) (95% CI)
Primary outcome (Cardiovascular death, MI, Stroke)	582 (9.3%)	719 (11.4%)	20% (10.3, 27.9) P=0.00009
Co-primary outcome (Cardiovascular death, MI, Stroke, Refractory Ischemia)	1035 (16.5%)	1187 (18.8%)	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 were maintained throughout the course of the trial (up to 12 months).

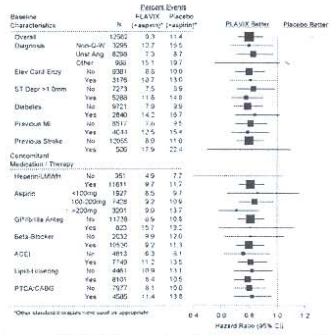
Figure 2. Cardiovascular Death, Myocardial Infarction, and Stroke in the CURE Study



* 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 (75-325mg 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).

INDICATIONS AND USAGE

PLAVIX (clopidogrel bisulfate) is indicated for the reduction of atherosclerotic 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 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.

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 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 17,500 clopidogrel-treated patients. In worldwide 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 antiplatelet 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 5 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. 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.

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.

PLAVIX®
clopidogrel bisulfate tablets

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: The safety of the coadministration of PLAVIX 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 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**), **antiepileptic agents, hormone replacement therapy, heparins** (unfractionated and LMWH) and **GPIIb/IIIa antagonists** without evidence of clinically significant adverse interactions. The use of oral anticoagulants, non-study anti-platelet drug and chronic NSAIDS was not allowed in CURE and there are no data on their concomitant use 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/m² 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/m² basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, PLAVIX should be used during pregnancy only if clearly needed.

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 17,500 patients, including over 9,000 patients treated for 1 year or more. 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. The clinically important adverse events observed in CAPRIE and CURE are discussed below.
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 3). 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%), was the same in both groups.
In patients receiving both PLAVIX and aspirin in CURE, the incidence of bleeding is described in Table 3.

Table 3: 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: <100mg=2.6%; 100-200mg= 3.5%; >200mg=4.9%
§ Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100mg=2.0%; 100-200mg= 2.3%; >200mg=4.0%
¶ 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.
Neutropenia/agranulocytosis: Ticlopidine, a drug chemically similar to PLAVIX, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/µL). In CAPRIE severe neutropenia was observed in six patients, four on PLAVIX and two on aspirin. Two of the 9599 patients who received PLAVIX and none of the 9586 patients who received aspirin had neutrophil counts of zero. One of the four PLAVIX patients in CAPRIE was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with PLAVIX (clopidogrel bisulfate). In CURE, the numbers of patients with thrombocytopenia (19 PLAVIX+ aspirin vs 24 placebo + aspirin) or neutropenia (3 vs 3) were similar.
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 in the CAPRIE trial. In the CURE trial the incidence of these gastrointestinal events for patients receiving PLAVIX + aspirin was 11.7% compared to 12.5% for those receiving placebo + aspirin.
In the CAPRIE trial, the incidence of peptic, gastric or duodenal ulcers was 0.7% for PLAVIX and 1.2% for aspirin. In the CURE trial the incidence of peptic, gastric or duodenal ulcers was 0.4% for PLAVIX + aspirin and 0.3% for placebo + aspirin.
Cases of diarrhea were reported in the CAPRIE trial 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%). In the CURE trial, the incidence of diarrhea for patients receiving PLAVIX + aspirin was 2.1% compared to 2.2% for those receiving placebo + aspirin.
In the CAPRIE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for PLAVIX and 4.0% for aspirin. In the CURE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 0.9% for PLAVIX + aspirin compared with 0.8% for placebo + aspirin.
Rash and Other Skin Disorders: In the CAPRIE trial, 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). In the CURE trial the incidence of rash or other skin disorders in patients receiving PLAVIX + aspirin was 4.0% compared to 3.5% for those receiving placebo + aspirin.
In the CAPRIE trial, 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. In the CURE trial, the incidence of patients withdrawing because of skin and appendage disorders adverse reactions was 0.7% for PLAVIX + aspirin compared with 0.3% for placebo + 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.

Table 4: Adverse Events Occurring in ≥2.5% of PLAVIX Patients in CAPRIE

Body System / Event	% Incidence (% Discontinuation) 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				
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				
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.
Adverse events occurring in ≥2.0% of patients on PLAVIX in the CURE controlled clinical trial are shown below regardless of relationship to PLAVIX.

Table 5: Adverse Events Occurring in ≥2.0% of PLAVIX Patients in CURE

Body System / Event	% Incidence (% Discontinuation) PLAVIX (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)
Body as a Whole–general disorders		
Chest Pain	2.7 (<0.1)	2.8 (0.0)
Central & peripheral nervous system disorders		
Headache	3.1 (0.1)	3.2 (0.1)
Dizziness	2.4 (0.1)	2.0 (<0.1)
Gastrointestinal system disorders		
Abdominal pain	2.3 (0.3)	2.8 (0.3)
Dyspepsia	2.0 (0.1)	1.9 (<0.1)
Diarrhea	2.1 (0.1)	2.2 (0.1)

*Other standard therapies were used as appropriate.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving PLAVIX (clopidogrel bisulfate) in the CAPRIE or CURE 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 CURE).
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 CAPRIE or CURE 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 CURE) .
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. *Urinary system disorders:* Abnormal renal function, acute renal failure. *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: fever, 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 was reported in the large, CAPRIE 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
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 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**).
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) 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]

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