ON THE BEAT

Cardiologists on the Move

Dr. Gordon Tomaselli, an expert on sudden cardiac death and heart rhythm disturbances, has been appointed direc-



DR. GORDON TOMASELLI

tor of Johns Hopkins University School of Medicine's division of cardiology in Baltimore.

As a cardiac electrophysio-Dr. logist, Tomaselli has worked to determine what factors are predic-

tive of success with implanted cardiac defibrillators.

In his new role, Dr. Tomaselli is expected to concentrate on early detection of arrhythmia using imaging, genetic screening, and applications of stem cell technology in damaged heart tissue.

After earning an undergraduate degree at the State University of New York at Buffalo and a medical degree from Albert Einstein College of Medicine in the Bronx, N.Y., Dr. Tomaselli completed a residency at University of California at San Francisco. He went on to join the Cardiovascular Research Institute there before moving to the fellowship program at the Johns Hopkins School of Medicine in 1986. He joined the faculty at Hopkins 3 years later.

Dr. Tomaselli will continue as codirector of the Donald W. Reynolds Cardiovascular Clinical Research Center at Hopkins. In his new post, he succeeds Dr. Eduardo Marbán, who led the division since 2002 and will remain active as adjunct faculty.

Dr. Edward Kasper has been named the new clinical director of Johns Hopkins University School of Medicine's division of cardiology, and codirector of



DR. EDWARD KASPER

the school's Heart and Vascular Institute, along with Dr. Tomaselli.

Dr. Kasper received his undergraduate degree from Johns Hopkins 1979. After receiving his medical degree at

the University of Connecticut, Farmington, he returned to his alma mater in 1987 to be a faculty instructor in medicine. He completed his cardiology specialization at JHU in 1991 and-after another brief sojourn at Vanderbilt University in Nashville, Tenn.—returned to Hopkins for good in 1993 to head up the university's transplant program transplant and organ rejection issues being one of Dr. Kasper's primary fields of interest. Another area of research for Dr. Kasper is the biological origins of heart failure.

For the last 5 years, Dr. Kasper has been the director of cardiology at Johns Hopkins Bayview Medical Center, the

second-largest hospital in the Johns Hopkins Health System, where he tripled the number of faculty and staff.

In his new position, Dr. Kasper succeeds Dr. Richard Lange, who will remain on staff as adjunct faculty.

Dr. Ronald G. Victor has been named associate director for clinical research in the Cedars-Sinai Heart Institute in Los Angeles. He will also serve as director of the Cedars-Sinai Hypertension Center.

A primary area of research for Dr Vic-

tor is in hypertension in African Americans. Most recently he has been involved in a Dallas-area study to evaluate whether barbershops can be used for community health promotion programs targeting hypertension in African American men.

Dr. Victor also is well known for his work with the National Institute on Drug Abuse, attempting to find an emergency antidote for cocaine overdose patients.

Dr. Victor earned his medical degree from Tulane University in New Orleans, and completed his residency in internal medicine at University of California, Los Angeles.

He completed fellowships in cardiology, cardiovascular research, and neurophysiology at Duke University, Durham, N.C.; the University of Iowa, Iowa City; and the University of Uppsala in Sweden, respectively.

Since 1986, Dr. Victor has been a member of the faculty and then a professor of medicine at the University of Texas Southwestern Medical Center in Dallas. Most recently, he has held the title of codirector at Donald W. Reynolds Cardiovascular Clinical Research Center there.

—Denise Napoli

$\textbf{PLAVIX}^{\text{(8)}}$ clopidogrel bisulfate tablets

INDICATIONS AND USAGE
PLAVIX (clopidogrel bisulfate) is indicated for the reduction of atherothrombotic of

PLANK (lopidogrel bisulfate) is indicated for the reduction of atherothrombotic events as follows:

Recent MI, Recent Stroke or Established Peripheral Arterial Disease For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, PLAVIX has been shown to reduce the rate of a combined end-point of new ischemic stroke (falal or not), new MI (fatal or not), and other vascular death). Acute Coronary Syndrome

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

-for patients with ST-segment elevation acute myocardial infarction, PLAVIX has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

CONTRAINDICATIONS

The use of PLAVIX is contraindicated in the following conditions: Hypersensitivity to the drug substance or any component of the product. Active pathological bleeding such as peptic uter or intracranial hemorrhage.

WARNINGS

WARNINGS
Thrombotic thrombocytopenic purpura [TTP]:
TTP has been reported rarely following use of PLAVIX, sometimes after a short expo (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatincluding plasmapheresis (plasma exchange). It is characterized by thrombocytopomicroangiopathic hemohytic anemia (schistocytes [fragmented RBG] seen on peripl smear], neurological findings, renal dysfunction, and fever. [see ADVERSE REACTIONS]

PRECAUTIONS
General
PANTy prolongs the bleeding time and therefore should be used with caution in patients who nay be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAWX should be discontinued 5 days prior to surgery. Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see ADVIESS REACTIONS). In patients with recent TIA or stroke who are at high risk of recurrent ischemic events, the combination of aspirin and PLAVIX has not been shown to be more effective than PLAVIX alone, but the combination has been shown to increase major bleeding, and Slededing 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 of 3.3% 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 ulcres). Drugs that might induce such lesions should be used with caution in patients with severe hepatic disease, who may have bleeding diatheses. PLAVIX should be used with caution in this population.

topulation.

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

impairment. PLAVIX should be used with causion in this population.

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

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Drug Interactions
Study of specific drug interactions yielded the following results:
Aspirin: Aspirin did not modify the clopidoger-herelated 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 PLAWIX. PLAWIX and aspirin have been administered together for up to one year. Heparin: In a study in healthy volunteers, PLAWIX did not necessitate modification of the heparin dose or after the effect of heparin on coagulation. Coadministration of the parin had no effect on inhibition of platelet aggregation induced by PLAWIX.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of PLAWIX was associated with increased occult gastrointestinal blood loss. NSAIDs and PLAWIX should be coadministered with caution.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of Warfarin with PLAWIX was coadministered with actual on the proper of the properties of

actions. the concomitant use of oral anticoagulants, non study oral anti iic NSAIDs with clopidogrel.

Drug/Laboratory Test Interactions

None known. Carcinogenesis, Mutagenesis, Impairment of Fertility There was no evidence of tumorigenicity when dopidogrel was administered for 78 weeks to mice and 104 weeks to aits at dossages up to 77 mg/kg per day, which alforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg. Clopidogrel was not genotoxic in lour in vitro tests fames test, 104A-repair test in rat hepato-yets, egner mutation assay in Clinice hamsel finbroblass, and metaphase formonome analy-sis of human hymphocytes and in one in vivo test (micronucleus test by oral route in mice). Clopidogrel was found to have no effect on lertility of male and female rast at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m² basis). Prevenancy

Pregnancy
Pregna

Justing Mothers
Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk
ts not known whether this drug is excreted in human milk. Because many drugs are
xcreted in human milk and because of the potential for serious adverse reactions in nurs
gnifants, a decision should be made whether to discontinue nursing or to discontinue
he 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

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

Geriatric Use

Of the total number of subjects in the CAPRIE, CURE and CLARITY controlled clinical studies, approximately 59% of patients treated with PLAVIX were 65 years of age and older, and 5% were 75 years and older. In COMMIT, approximately 58% of the patients treated with PLAVIX were 60 years and older, 26% of whom were 70 years and older. The observed risk of thrombotic events with clopidager plus aspirin versus placebo plus aspirin by age category is provided in Figures 3 and 6 for the CURE and COMMIT trials, respectively (see CLINICAL STUDIES). The observed risk of bleeding events with dopidager plus aspirin by age suspirin by age sparin by age category is provided in Tables 5 and 6 for the CURE and COMMIT trials, respectively (see ADVERSE REACTIONS).

ADVERSE REACTIONS
PLAVIX has been evaluated for safety in more than 42,000 patients, including over 9,000 patients treated for 1 year or more. The clinically important adverse events observed in GAPRIE, CURE, CLARITY and COMMIT are discussed below. The overall tolerability of PLAVIX in CAPRIE was similar that aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions.

general and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. Hemorrhagic in CAPIEL 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 CIJER_PLAVIX use with aspirin was associated with an increase in bleeding compared to placebo with aspirin (see Table 5). There was an excess in major bleeding in patients receiving PLAVIX plus aspirin compared with packed by use aspirin, inprinarly agstorinestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fallal bleeding (0.2%), were the same in both groups.

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

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 Intraocular bleeding with	0.4	0.3	
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. +

**Standard Seeding event rate for PLAVIX. +

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**Sprinn by age were: <65 years = 2.5%, ≥65 to

**Z5 years = 4.1%, ≥75 years 5.9%

**Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin:

**C100 mg=2.0%: 100-200 mg= 2.3%: >200 mg=4.0%

**Major bleeding event rate for placebo + aspirin by age were: <65 years = 2.1%, ≥65 to

**Z5 years = 3.1%, ≥75 years 3.6%

**Led to interruption of study medication.

**Minimathus norzent 1078/ia of the nationals in the CURE study received heparin/LMWH, and

≥ 17 (sept.) = 3.1%, €2) yeard 3.20% [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% PLAWK + 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 PLAWX + aspirin, and 6.3% for placebo + aspirin. In CLARITY, the incidence of major bleeding (defined as intracranial bleeding of bleeding associated with a fall in hemoglobin > 5 g/dl) was similar between groups (1.3% versus 1.1% in the PLAWX + aspirin and in the placebo + aspirin groups, respectively). This was 1.5% in the PLAWX + aspirin and in the placebo + aspirin groups, respectively have successfully and intracranial hemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups as shown in Table 6 below.

Table 6: Number (8) of Patients with Bleeding Events in COMMIT

ar in both groups as shown in Table 6 below. Table 6: Number (%) of Patients with Bleeding Events in COMMIT

134 (0.6%)	125 (0.5%)	0.59
82 (0.4%)	73 (0.3%)	0.48
36 (0.2%)	37 (0.2%)	0.90
55 (0.2%)	56 (0.2%)	0.91
39 (0.2%)	41 (0.2%)	0.81
831 (3.6%)	721 (3.1%)	0.005
896 (3.9%)	777 (3.4%)	0.004
	36 (0.2%) 55 (0.2%) 39 (0.2%) 831 (3.6%) 896 (3.9%)	36 (0.2%) 37 (0.2%) 55 (0.2%) 56 (0.2%) 39 (0.2%) 41 (0.2%) 831 (3.6%) 721 (3.1%)

* Major bleeds are cerebral bleeds or non-cerebral bleeding was independent of age.
** The relative rate of major noncerebral or cerebral bleeding was independent of age.
Event rates for PLAVIX + aspirin by age were: <60 years = 0.3%, ≥60 to <70 years = 0.7%,
≥70 years 0.8%, ≥70 years 0.7%.

*> 270 years 0.9%, ≥70 years 0.7%.

*> Adverse events occurring in 72.5% of patients on PLAVIX in the CAPRIE controlled dinical trial are shown below regardless of relationship to PLAVIX. The median duration of therapy was 20 months, with a maximum of 3 years.

**Table 7: Adverse Events Occurring in ≥2.5% of PLAVIX Patients in CAPRIE
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	% Incidence (% Discontinuation)		
Body System Event	PLAVIX [n=9599]	Aspirin [n=9586]	
Body as a Whole – general disorders			
Chest Pain	8.3 (0.2)	8.3 (0.3)	
Accidental/Inflicted Injury	7.9 (0.1)	7.3 (0.1)	
Influenza-like symptoms	7.5 (<0.1)	7.0 (<0.1)	
Pain	6.4 (0.1)	6.3 (0.1)	
Fatigue	3.3 (0.1)	3.4 (0.1)	
Cardiovascular disorders, general			
Edema	4.1 (<0.1)	4.5 (< 0.1)	
Hypertension	4.3 (<0.1)	5.1 (< 0.1)	
Central & peripheral nervous system disorders			
Headache	7.6 (0.3)	7.2 (0.2)	
Dizziness	6.2 (0.2)	6.7 (0.3)	
Gastrointestinal system disorders			
Any event	27.1 (3.2)	29.8 (4.0)	
Abdominal pain	5.6 (0.7)	7.1 (1.0)	
Dyspepsia	5.2 (0.6)	6.1 (0.7)	
Diarrhea	4.5 (0.4)	3.4 (0.3)	
Nausea	3.4 (0.5)	3.8 (0.4)	
Metabolic & nutritional disorders			
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)	
Musculo-skeletal system disorders			
Arthralgia	6.3 (0.1)	6.2 (0.1)	
Back Pain	5.8 (0.1)	5.3 (<0.1)	
Platelet, bleeding, & clotting disorders			
Purpura/Bruise	5.3 (0.3)	3.7 (0.1)	
Epistaxis	2.9 (0.2)	2.5 (0.1)	
Psychiatric disorders			
Depression	3.6 (0.1)	3.9 (0.2)	
Respiratory system disorders			
Upper resp tract infection	8.7 (<0.1)	8.3 (<0.1)	
Dyspnea	4.5 (0.1)	4.7 (0.1)	
Rhinitis	4.2 (0.1)	4.2 (< 0.1)	
Bronchitis	3.7 (0.1)	3.7 (0)	
Coughing	3.1 (<0.1)	2.7 (<0.1)	
Skin & appendage disorders			
Any event	15.8 (1.5)	13.1 (0.8)	
Rash	4.2 (0.5)	3.5 (0.2)	
Pruritus	3.3 (0.3)	1.6 (0.1)	
Urinary system disorders			
Urinary tract infection	3.1 (0)	3.5 (0.1)	

o additional clinically relevant events to those observed in CAPRIE with a frequency 5%, have been reported during the CURE and CLARITY controlled studies. COMMIT lected only limited safety data.

collected only limited safety data.

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

to that in patients receiving aspirin (in CAPIRE) or placebo + aspirin (in the other clinical trials).

Autonomic Nervous System Disorders: Syncope, Palpitation. Body as a Whole-general Gisorders: Sathenia, Fever, Hernia. Cardiovascular disorders: Cardiac failure: Central and peripheral nervous system disorders: Granps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertigo. Castrioutestrala system disorders: Granps legs, Hypoaesthesia, Neuralgia, Paraesthesia Siorders: Fibrillation atrial. Liver and biliary system disorders: Hepatic enzymes increased. Metabolic and nutritional disorders: Gout, hyperuricenian, non-protein intogen (IMPN) increased. Musculo-Skeletal system disorders: Arthritis, Arthrosis. Platelet, bleeding & clotting disorders: Gl hemorrhage, hematoma, platelets decreased. Psychiatric disorders. Anately, Insominia. Red blood cell disorders: Annemia. Respiratory system disorders. Systim. Siorders (2nd ilisarders). Annemia. Repriatory system disorders: Systim. Siorders (2nd ilisarders). Annemia. Repriatory system disorders. Systim Siorders (2nd ilisarders). Cartact, Conjunctivitis.

Other potentially serious adverse events which may be of clinical interes but were arely exported (1=30) in patients who received PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in the other clinical trials).

similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in the other clinical trials). Body as a whole: Allergic reaction, necrosis ischemic. Cardiovascular disorders: Edema generalized. Gastrointesimal system disorders: Peptic, gastric or duodenal uleer, gastriis, gastric uleer perforated, gastriis hemorrhagie, Lupper Gl uleer hemorrhagie. Liver and Biliary system disorders: Bilirubinemia, hepatitis infectious, liver fatty. Platelet, bleeding and clotting disorders: hemarthosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retropertioneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia. Red blood cell disorders: Anemia aplastic, anemia hypochromic. Reproductive disorders; fernale: Menorrhaga. Respiratory system disorders: Hemothorax. Skin and appendage disorders: Bullous eruption, rash erythematous, rash maculopapular, urticaria. Urinary system disorders. Ahnormal renal function, acute renal failure. White cell and reticuloendothelial system disorders: Saranulocytosis, granulocytopenia, leukemia, leukopenia, neutropenia.

Postmarketing Experience
The following events have been reported spontaneously from worldwide postmarketing

- Body as a whole:
 -hypersensitivity reactions, anaphylactoid reactions, serum sickness
 -central and Peripheral Nervous System disorders:
 -onfusion, hallucinations, taste disorders:
 -thepato-biliary disorders:
 -thepato-biliary disorders:
 -thepato-biliary disorders:
 -theoretical liver function test, hepatitis (non-infectious), acute liver failure
 -Platelet, Beeding and Clotting disorders:
 -cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitional hemorrhage)
 -thrombotic thrombocytopenic purpura (TTP) some Cases with fatal outcome (see WARNING).

DVERDOSAGE

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorspecies.
Idations About Specific Treatment:

OOSAGE AND ADMINISTRATION

The recommended daily uose of the transparency of the Coronary Syndrome (unstable angina/non-Q-wave MI), PLAVIX should be initiated with a single 300-mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with PLAVIX. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely (see CLINICAL STUDIES).

For patients with 57-segment elevation acute myocardial infarction, the recommended dose of PLAVIX is 75 mg once daily, administered in combination with aspirin, with or without thrombolytics, PLAVIX may be initiated with or without a loading dose (300 mg

without thrombolytics. PLAVIX may be initiated with or without a loading dose (300 mg was used in CLARIY; see CLINICAL STUDIES).
PLAVIX can be administered with or without lood.
No dosage adjustment is necessary for elderly patients or patients with renal disease. (See Clinical Pharmacology; Special Populations.)

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stributed by: stol-Myers Squibb/Sanofi Pharmaceuticals Partnership idgewater, NJ 08807

Brief Summary of Prescribing Information Revised October 2007

