

EMERGENCY MEDICINE'S ONLY INDEPENDENT NEWS MAGAZINE

Petition Demands Due Process Rights for EPs

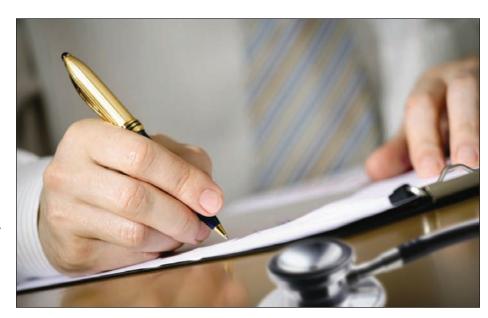
By Ruth SoRelle, MPH

petition that supports the due process rights of emergency physicians represents the core issue of the American Academy of Emergency Medicine and deserves the support of all emergency physicians, said its originator.

"I can't tell you how many times my heart would sink and my stomach would get sick listening to emergency physicians who were terminated for raising quality of care issues," said Robert McNamara, MD, a founding president of AAEM who recently ended his service on the board. "They were complaining about things that compromise their ability to care for patients — inadequate nursing staff, inappropriate policies. They were told to keep quiet, or they would be terminated."

As Dr. McNamara's last initiative before ending his service on AAEM's Board of Directors, he drafted a petition to galvanize emergency physicians into fighting for what he called a long overdue fight. The petition, posted on www.aaem. org/dueprocess/petition/, reads:

"We, the undersigned emergency physicians of this country, believe that



due process is fundamental to our ethical mandate to care for our patients without being pressured by administrative or other external influences. We serve as direct advocates for our patients, many of whom go to emergency departments because they are vulnerable due to medical, social or financial issues outside of their control. In some cases, such advocacy may conflict with profit-driven or other non-patient-oriented forces.

Therefore, we strongly oppose the contractual trend that allows hospitals or contract holders to terminate physicians without a fair hearing, since this hinders our ability to act at all times in the best interest of our patients."

Dr. McNamara's name appears first on the long list of emergency physicians who have signed the petition, and he said he hopes that thousands will follow suit. *Continued on page 11*

Out of the Pharmacy, Into the ED

By Angela Munasque

If you're looking for Janine Shipley, PharmD, a pharmacist at Licking Memorial Hospital in Newark, OH, you won't find her in the pharmacy filling medication orders behind the counter. You'll find her on the floor in the emergency department working right beside the physicians and nurses.

Ms. Shipley is a rare breed. Only three to five percent of EDs in the nation have a pharmacist on staff, according to May-Lee Robertson, DO, the medical director of the emergency department at Licking Memorial. Dedicated to the ED since February, Ms. Shipley has already proved to be an invaluable part of the team. She reconciles medications, consults with staff on treatment plans, and even completes paperwork to help patients adhere to therapies once they leave the ED.

So far, having a pharmacist in the ED is working well, but it's a program in its infancy, and there are kinks still to be ironed out. And for EDs who don't have a pharmacist but want one, even more challenges await them.

Patient Safety

It's easy to understand why an ED might $Continued\ on\ page\ 20$

SPECIAL REPORT

The Great Stroke Debate For more than a decade, the buzz in emergent stroke care has been fueled by three letters: tPA. But there's more to stroke care than thrombolytics.

VIEWPOINT
toxicology rounds $\dots \dots 4$
quick consult $\hdots 4$
${\it legal notes} \dots \dots .5$
${\tt JOURNAL~SCAN~\dots}$
Second opinion $\dots 17$
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ED PHARMACIST

Continued from page 1

want a pharmacist on hand. The Institute of Medicine found that EDs have the highest rate of preventable adverse events in the hospital, with nearly four million annually. (To Err is Human: Building a Safer Health System. Washington D.C.: National Academy Press; 1999.) Loud, crowded, and hectic, the environment of an ED can propagate mistakes, which has prompted hospitals to ramp up patient safety efforts in recent years.

The decision to add an emergency pharmacist at Licking Memorial was not a response to a specific situation, said Robert Montagnese, the hospital's president and chief executive officer, but rather a proactive move to improve quality of care.

Having a pharmacist on hand, Dr. Robertson said, to screen for negative interactions and formulate proper dosages boosts safety in the ED. And when the pharmacist is doing what she does best, physicians are able to devote more time to patient care, resulting in better role specialization and resource utilization.

Rollin (Terry) Fairbanks, MD, the principal investigator at the Emergency Pharmacist Research Center (EPRC) and an assistant professor of emergency medicine at Rochester (NY) University, is quick to point out what an emergency pharmacist's role is — and what it is not. "I think sometimes people who are not familiar with the program picture a pharmacist in the ED as someone dispensing drugs in a little room, and that's not at all what their role is," he said. The pharmacist's consultations on resuscitation, trauma, and other critical patients are crucial. "They're at the bedside. They're true clinical partners to us," he said.

As part of his work with EPRC, Dr. Fairbanks found that medical and nursing staff overwhelmingly value emergency pharmacists: 99 percent of respondents said pharmacists improve quality of care, 96 percent said pharmacists are an integral part of the care team, and 93 percent had consulted the pharmacist at least a few times during their past five shifts. (Emerg Med J 2007;24:716.)

Challenges Galore

As much as an emergency pharmacist contributes, there seem to be twice as many challenges to overcome. Licking Memorial, for one, would like to have more than one pharmacist in its ED. Pharmacists, however, "are not cheap," said Daniel Hays, PharmD, an emergency pharmacist with EPRC, and the current pharmacist shortage doesn't help matters. From 1998 until 2000, pharmacist vacancies ballooned from 2700 to 7000, according to the Health Resources and Services Administration. (The Pharmacist Workforce: A Study of the Supply and Demand for Pharmacists. Rockville, MD: Department of Health and Human Services; 2000.) A more recent study concluded that there was a "sustained unmet demand for pharmacists" in the United States from 1999 through 2003. (Am J Health Syst Pharm 2005;62:492.)

Assuming that an ED can get its hands on a pharmacist, they'll have to convince administration about their need for one, of course, which can prove difficult, said Drs. Hays and Fairbanks. "Hospital leadership wants to see a business model," Dr. Fairbanks said, and not just any business model, but one that will create a "return of investment."

The good news for EDs interested in having their own pharmacist is that there are descriptive papers that record ways that pharmacists have saved costs, and the EPRC provides access to many of these. (www.emergencypharmacist.org.) Luckily for Licking Memorial, administration was not an antagonist in implementing this initiative — just the opposite, in fact. "Upper management wholeheartedly supported and pushed us actually," said Jean Glaser, PharmD, the director of the pharmacy at Licking Memorial.

Once an ED finds a pharmacist and administration approves, challenges still have to be conquered. A Joint Commission policy on medical reconciliation that requires a pharmacist to review all orders could tie up emergency pharmacists, preventing them from doing clinical consultations and prospective medicine reviews, said Dr. Fairbanks. (EMN 2007;29:1.)

Beyond this, everyone is concerned about educational support for these vanguard pharmacists, and for EDs who want to follow their path. "It is definitely a new adventure, and without the right direction," Dr. Glaser cautioned, "they perhaps aren't going to capture everything they need to be thinking about or do things in the best manner."

Comments about this article? Write to EMN at emn@lww.com.

PLAVIX® clopidogrel bisulfate tablets

INDICATIONS AND USAGE

PLANX (dopidogrel bisulfate) is illustrated for the property of the property o

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

cular death, MI, stroke, or refractory ischemia. r patients with ST-segment elevation acute myocardial infarction, PLAVIX has been wn 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 ive primary angioplasty.

CONTRAINDICATIONS

INTRAINDICATIONS

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

WARNINGS
Thrombotic thrombocytopenic purpura (TTP):
TTP has been reported rarely following use of PLAVIX, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemohytic anemia (schistocytes (fragmented R86); seen on periodiation and rever. (See ADVERSE REACTIONS.)

PREVAUTIONS
General
PLAVIX prolongs the bleeding time and therefore should be used with caution in patients who
may be at risk of increased bleeding from trauma, surgery, or other pathological conditions
(particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an
antiplatelet effect is not desired, PLAVIX should be discontinued 5 days pror to surgery.
Due to the risk of bleeding and undesirable hematological effects, blood cell count determi-nation and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see ADVERSE REACTIONS).
In patients with recent Tak or stoke who are at high risk of recurrent ischemic events,
the combination of aspirin and PLAVIX has not been shown to be more effective than
PLAVIX alone, but the combination has been shown to increase major bleeding.
GI Bleeding. In CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of
SLOW, vs. 2.7% on a spirin. 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 Hepaticistyl Impaired Patients: Experience is limited in patients with severe hepatic Use in Hepatically Impaired Patients: Experience is limited in patients with severe he disease, who may have bleeding diatheses. PLAVIX should be used with caution i

Justian Incompleted 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 ABUSINESS. THE PLAVIX SHOULD BE HEAVED. THE PLAVIX SHOULD BE ABUSED. THE PLAVIX OF PLAVIX COMBINED WHEN PLAVIX OF PLAVIX COMBINED WITH PLAVIX COMBINED WITH PLAVIX COMBINED WHEN PLA

known to affect bleeding before any surgery is scheduled and before any new drug is taken. **Drug Interactions**Study of specific drug interactions yielded the following results:
Aspinia: Aspinin did not modify the clopidoged-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 PAUK. PLAVIX protentiated the effect of aspini on collagen-induced platelet aggregation. PLAVIX and aspirin have been administered together for up to one year. Plate approach in the Platelia approach in the plate of the plate 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, INSAIDS; in healthy volunteers receiving naproxen. concomitant administration of PLAVIX was associated with increased occult gastrointestinal blood loss. NSAIDs and PLAVIX should be coadministered with caution. Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with PLAVIX should be undertaken with caution. [see PRECAUTIONS-General]. Other Concomitant ant Therapy. No dirically significant pharmacodynamic interactions were

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions wer observed when PLAVIX was coadministered with atenolol, nifedipine, or both atenolo and nifedipine. The pharmacodynamic activity of PLAVIX was also not significant influenced by the coadministration of phenobarbital, cimetidine or estrogen. and nifedipine. The pharmacodynamic activity of PLAVIX was also not significantly influenced by the coadministration of **phenobarbital**, cimeldine or **estrogen**. The pharmacokinetics of **digoxin** or **theophylline** were not modified by the coadministration of PLAVIX (dopidogrel bisulfate). At high concentrations in *vitra*, optioplogrel inhibits P₁₇₀ (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 PAUNX.

In addition to the above specific interaction studies, patients entered into clinical trials

In PLAVX received a variety of concomilant medications including diuretics, beta-cking agents, angiotensin converting enzyme inhibitors, calcium antagonists, polesterol lovering agents, coronary vasodilators, antidiabetic agents (including ulin), thrombolytics, heparins (unfractionated and LMWH), GPIIb/IIIa antagonists,

on the concomitant use of oral anticoagulants, non study oral anti nronic NSAIDs with clopidogrel.

Drug/Laboratory Test Interactions

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of turnorigenicity when clopidogrel was administered for 78 weeks to mix an o evidence of turnorigenicity when clopidogrel was administered for 78 weeks to mix and 104 weeks to raits at diosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended dayl dose of 75 mg. In Chipdogrel was not genotoxic in four in vitro tests himes test, DNA-repair test in rait hepatocytes, gene mutation assay in Chinese hanster fibroblasts, and metaphase chromosome analysis of human hymphotycis) and in one in vivo test (incronucleus test to not a result in mixed.)

mphocytes) and in one *in vivo* test (micronucleus test by oral route in mice). as 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
Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up
production of the production studies are not always predictive of a human response, PAVIX should be used during pregnancy only if clearly needed.

ursing 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. 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 unsing 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.

Salety and effectiveness in the pediatric population have not been established. Geriatric Use
Of the total number of subjects in the CAPRIE, CURE and CLARITY controlled clinical studies, approximately 50% of patients treated with PLAVIX were 65 years of age and older, and
15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with
PLAVIX were 60 years and older, 26% of whom were 70 years and older. The observed risk of thrombotic events with clopidogref plus aspirin versus placebo plus
aspirin by age category is provided in Figures 3 and 6 for the CUE and COMMIT trials,
respectively (see CLINICAL STUDIES). The observed risk of bleeding events with clopidogref
plus aspirin versus placebo plus aspirin by age category is provided in Tables 5 and 6 for
the CURE and COMMIT trials, respectively (see ADVERSE REACTIONS).

ADVERSE REACTIONS

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 CAPBIE, CURE, CLARITY and COMMIT are discussed below. The overall tolerability of PLAVIX in CAPBIE was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. Hemorrhagic in CAPBIE patients receiving PLAVIX, gastrointestinal hemorrhage occurred at 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 a placebo with aspirin (see Table 5). There was an excess in major bleeding in patients receiving PLAVIX plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fatal bleeding (0.2%), were the same in both groups.

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

PLAVIX and aspirin in CURE.				
Table 5: CURE Incidence of bleeding complications (% patients)				
Event	PLAVIX (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)	P-value	
Major bleeding †	3.7 ‡	2.7 §	0.001	
Life-threatening bleeding	2.2	1.8	0.13	
Fatal	0.2	0.2		
5 g/dL hemoglobin drop	0.9	0.9		
Requiring surgical intervention	0.7	0.7		
Hemorrhagic strokes	0.1	0.1		
Requiring inotropes	0.5	0.5		
Requiring transfusion (≥4 units)	1.2	1.0		
Other major bleeding	1.6	1.0	0.005	
Significantly disabling 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

Fatal

her noncerebral bleeding (non-major)

* Other standard therapies were used as appropriate.
† Life threatening and other major bleeding.
‡ Major bleeding event rate for PLAVIX + aspirin was dose-dependent on aspirin:
<100 mg=2.6%; 100.20 mg=3.5%; ≥00 mg=4.9%
Major bleeding event rate for PLAVIX + aspirin by age were: <65 years = 2.5%, ≥65 to
<7.5 years = 4.1%, ≥75 years 5.9%
Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin:
<100 mg=2.0%; 100-200 mg=2.3%; ≥000 mg=4.0%
Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, ≥65 to
<7.5 years = 3.1%, ≥75 years 3.6%
Led to interruption of study medication.
Ninety-two percent [929] 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 dasp spir for 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.

days of bypass graft surgery, the event rate was 9.6% for PLAVIX + aspirin, and 6.3% for placebo + aspirin.dence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in hemoglobin > 5 g/dl) was similar between groups (1.3% versus 1.1% in the PLAVIX + aspirin and in the placebo + aspirin groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytics or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the PLAVIX + aspirin and in the placebo + aspirin groups, respectively) and intrachal hemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups. The overall rate of noncerbral major bleeding or crebral bleeding in COMMIT was low and similar in both groups as shown in Table 6 below.

Table 6: Number (%) of Patients with Bleeding Events in COMMIT Type of bleeding PLAVIX Placebo P-value (+ aspirin) (N=22891) (+ aspirin) (N=22961) 0.48 0.90 0.91 norrhagic stroke

41 (0.2%

721 (3.1%) 777 (3.4%) 0.004 y noncerebral bleeding

The relative that an experience of the properties of the relative that the state of major noncerebral or cerebral bleeding was independent of age, went rates for PLAVIX + aspirin by age were: <60 years = 0.3%, 260 to <70 years = 0.7%, 70 years = 0.6%, 270 years =

<70 years = 0.6%, 270 years 0.7%. Adverse events occurring in ≥25% 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 year. Table 7: Adverse Events Occurring in ≥2.5% of PLAVIX Patients in CAPRIE

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

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

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

rials). Autonomic Nervous System Disorders: Syncope, Palpitation. Body as a Whole-general disorders: Asthonia Enwer Hamis Cardiovascular disorders: Cardiac failure, Central and disorders: Asthenia, Fever, Hernia. Cardiovascular disorders: Cardiac failure. Central and peripheral nervous system disorders. Cramps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertiga. Gastroinestinal system disorders: Costispation, Vomiting, Heart rate and rhythm disorders: Fibrillation atrial. Liver and biliary system disorders: Hepatic enzymes increased. Metabolic: and untitional disorders: Gout, hyperuricemia, non-protein nitrogen (NPN) increased. Musculo-skeletal system disorders: Arthritis. Arthrosis. Platelet, bleeding & cotting disorders: Gle hemorrhage, hematoma, platelets decreased. Psychiatric disorders: Anxiety, Insomnia. Red blood cell disorders: Anemia. Respiratory system disorders: Pneumonia, Simusitis. Skin and appendage disorders: Eczema, Skin ulceration. Ulmary system disorders: Cystitis. Vision disorders: Cataract, Conjunctivitis. Other potentially serious adverse events which may be of clinical interest but were rarely reported (1-49) in patients who received PLAVIX in the controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was smillar to that in patients receiving assirin fin CARREIE or placebo+ a sopirin (in the other

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. Gastrointesiinal system disorders: Peptic, gastric or duodenal ulere, gastriis, gastric ulere periorated, gastriis hemorrhagic, upper GI ulere hemorrhagic. Liver and Biliary system disorders: Bilirubinemia, hepatitis infectious, liver fatty. Platelet, bleeding and dolting disorders: hemarthrosis, hematuria, hemophysis, hemorrhage intracanial, hemorrhage operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia. Red blood cell disorders. Anemia aplastic, anemia hypothyromic. Reproductive disorders, Fenale: Menorrhaga. Respiratory system disorders: Hemothoras. Skin and appendage disorders: Bullous eruption, rash erythematous, rash maculopapular, urticaria. Urinary system disorders Abnormal renal function, acute renal failure. White cell and reticulendothelial system disorders: Agentulocytosis granulocytopenia leukemia leukonenia neutronenia.

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

Central and Peripheral Nervous System disorders:
-confusion, hallucinations, taste disorders
-confusion, hallucinations, taste disorders
-confusion, hallucinations, taste disorders
-abnormal liver function test, hepatibilis (non-infectious), acute liver failure
District. Illustrict and clienting disorders:

Platelet, Bleeding and Clotting disorders: cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage)

thrombotic thrombocytopenic purpura (TTP) — some cases with fatal outcome — (see **WARNING**)

agranulocytosis, aplastic anemia/pancytopenia conjunctival, ocular and retinal bleeding

-conjunctival, ocular and retinal bleeding Respiratory, thoraci and mediastinal disorders:
 -bronchospasm, interstitial pneumonitis
 Skin and subcutaneous tissue disorders:
 -angioedema, eyythema multiforme, Stevens-Johnson syndrome, toxic epidermal

-angioedema, erythema multiforme, Steve necrolysis, lichen planus
 - Renal and urinary disorders: glomerulopathy, increased creatinine levels
 - Vascular disorders:

- vasculitis, hypotension
- Gastrointestinal disorders:
- colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis
- Musculoskeletal, connective tissue and bone disorders:

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 lehal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vormiting (in baboons), prostration, difficult breathing, and gastrointestinal hemor-thogo in all specified. were vomiting (in baboons), prostration, difficul rhage in all species. Recommendations About Specific Treatment:

Recommendations Apolus Specinic Treatments
Based on biological plausibility, platelet transfusion may
pharmacological effects of PLAVIX if quick reversal is requir

DOSAGE AND ADMINISTRATION

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease
The recommended daily dose of PLAVIX is 75 mg once daily.

Acute Coronary Syndrome
For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-C-wave MI), PLAVIX should be initiated with a single 300-mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg.3.25 mg once daily) should be initiated and continued in combination with PLAVIX. In CURE, most patients with Acute Coronary

and continued in combination with PLAVIX. In CURE, most patients with Acute coronary Syndrome also received hepain acutely (sec CUINCLA STUDIES). For patients with ST-segment elevation acute myocardial infarction, the recommended dose of PLAVIX is 75 mg once daily, administered in combination with aspirin, with or without thrombolytics. PLAVIX may be initiated with or without a loading dose (300 mg

was used in CLARITY; see **CLINICAL STUDIES**).
PLAVIX can be administered with or without food.
No dosage adjustment is necessary for elderly pa
(See **Clinical Pharmacology: Special Populations**. u. patients or patients with renal disease

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Brief Summary of Prescribing Information Revised October 2007