

Regulation of Off-Label Drugs Warrants Attention

BY JOYCE FRIEDEN
Senior Editor

PHILADELPHIA — The Food and Drug Administration needs to change the way it regulates promotion of off-label drug use, according to the chair of the department of health policy and public health at the University of the Sciences in Philadelphia.

This year, the FDA issued draft guidance regarding off-label promotion. The draft guidance states that although any materi-

als promoting off-label use must be peer reviewed, approval by the agency is not required, and the pharmaceutical company does not need to prove its intent to submit a new drug application for the off-label use, Robert I. Field, J.D., Ph.D., said at a meeting of the American Society of Law, Medicine, and Ethics. “This is considered to be a significant loosening of the requirements, certainly of the FDA’s enforcement attitude.”

However, the company must clearly dis-

close that the suggested use is off-label, and any published negative findings regarding the off-label use must be included in the materials. “The problem is, negative findings don’t get published very often, so there’s probably not going to be a whole lot of that,” he added.

The comment period on the FDA’s draft guidance ended several months ago; final guidance has yet to be issued. But there are certainly reasonable arguments for promoting off-label use under certain

circumstances, according to Dr. Field.

“Medicine only advances when information is shared, “and there are good reasons to allow off-label uses and therefore to allow physicians to know about those off-label uses,” he said. “On the other hand, it is clear that lack of oversight will lead to overzealous, aggressive promotion of uses that have limited, if any, scientific substantiation. The big question [is whether the] average physician who’s working 80 hours a week [is] really going to be able to evaluate this information, even if it has a disclosure written at the top.”

Although the ultimate goal should be to get approval for an off-label use, pharmaceutical companies don’t have many good reasons to do so, Dr. Field noted. “The

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problem is that clinical trials take a lot of time and the FDA is an overburdened agency; its reviews are slow.” Off-label use is abundant and has increased over the last 3 decades, Dr. Field said.

Before 1997, the FDA opposed all off-label promotion. The agency allowed limited distribution of peer-reviewed articles in direct response to physician requests.

In 1997, Congress passed the Food and Drug Administration Modernization Act, which allowed pharmaceutical companies to initiate distribution of articles promoting off-label use if they came from a legitimate peer-reviewed source, such as a journal or book chapter. Also, companies could sponsor continuing medical education if it was done through a third-party operation.

But there were restrictions on these uses—the material to be distributed first had to be given to the FDA for approval, and the company had to intend to submit a new drug application for the off-label use.

In 1998, the Washington Legal Foundation sued the FDA, arguing that the restrictions on article distribution were unconstitutional under the First Amendment. The court said the agency could limit article distribution but could not require prior submission of the materials for FDA approval or require that the company intend to submit a new drug application. A similar lawsuit in 1999 produced the same result.

These rulings “left questions as to what would and wouldn’t be allowed” under the act, Dr. Field said.

Other challenges to off-label promotion rules were not as successful. In 2004, Pfizer Inc. was fined \$430 million for paying physicians to promote the off-label use of gabapentin (Neurontin) with little evidence of benefit. And a psychiatrist was arrested in 2006 for accepting \$100,000 to promote off-label uses for Jazz Pharmaceutical Inc.’s sodium oxybate (Xyrem). ■

PLAVIX® clopidogrel bisulfate tablets

Rx only

INDICATIONS AND USAGE

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

- Recent MI, Recent Stroke or Established Peripheral Arterial Disease**
For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, PLAVIX has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or non-fatal MI/fatal or non-fatal stroke) and other vascular death.
- Acute Coronary Syndrome**
For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, PLAVIX has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.
- For patients with ST-segment elevation acute myocardial infarction, PLAVIX has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

CONTRAINDICATIONS

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

WARNINGS

Thrombotic thrombocytopenic purpura (TTP)

TTP has been reported rarely following use of PLAVIX, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. (See ADVERSE REACTIONS.)

PRECAUTIONS

General

PLAVIX prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intracranial), if a patient is to undergo elective surgery and an antiplatelet effect is not desired. PLAVIX should be discontinued 5 days prior to surgery. Due to the risk of bleeding and undesirable hematologic effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see ADVERSE REACTIONS). In patients with recent TIA or stroke who are at high risk of recurrent ischemic events, the combination of aspirin and PLAVIX has not been shown to be more effective than PLAVIX alone, but the combination has been shown to increase major bleeding.

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

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

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

Information for Patients

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

Drug Interactions

Study of specific drug interactions yielded the following results:

Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by PLAVIX. PLAVIX potentiated the effect of aspirin on collagen-induced platelet aggregation. PLAVIX and aspirin have been administered together for up to one year.

Heparin: In a study in healthy volunteers, PLAVIX did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by PLAVIX.

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

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

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when PLAVIX was administered with **atenolol**, **nifedipine**, or both **atenolol** and **nifedipine**. The pharmacodynamic activity of PLAVIX was also not significantly influenced by the administration 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-gp (2C9). Accordingly, PLAVIX may interfere with the metabolism of **phenytoin**, **tamoxifen**, **tolbutamide**, **warfarin**, **rosteramide**, **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 administered 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-blockers**, **angiotensin converting enzyme inhibitors**, **calcium antagonists**, **cholesterol lowering agents**, **coronary vasodilators**, **antidiabetic agents** (including **insulin**), **thrombolytics**, **heparins** (unfractionated and LMWH), **GPIIb/IIIa antagonists**, **antiepileptic agents** and **hormone replacement therapy** without evidence of clinically significant adverse interactions.

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

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures ≥ 25 times that in humans at the recommended daily dose of 75 mg. Clopidogrel was not genotoxic in *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.

Geriatric Use

Of the total number of subjects in the CAPRIE, CURE and CLARITY controlled clinical studies, approximately 50% of patients treated with PLAVIX were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with PLAVIX were 60 years and older, 26% of whom were 70 years and older. The observed risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Figures 3 and 6 for the CURE and COMMIT trials, respectively (see CLINICAL STUDIES). The observed risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Tables 5 and 6 for the CURE and COMMIT trials, respectively (see ADVERSE REACTIONS).

ADVERSE REACTIONS

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

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

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

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

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

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 intropes	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	
Intracranial bleeding with significant loss of vision	0.05	0.03	
Requiring 2-3 units of blood	1.3	0.9	
Minor bleeding ††	5.1	2.4	<0.001

* Other standard therapies were used as appropriate.

† Life threatening and other major bleeding.

‡ Major bleeding event rate for PLAVIX + aspirin was dose-dependent on aspirin: <100 mg=2.0%; 100-200 mg=2.3%; >200 mg=4.0%.

§ Major bleeding event rates for PLAVIX + aspirin by age were: <65 years = 2.5%, ≥65 to <75 years = 4.1%, ≥75 years 5.9%

¶ Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg=2.0%; 100-200 mg=2.3%; >200 mg=4.0%.

|| Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, ≥65 to <75 years = 3.1%, ≥75 years 3.6%

¶¶ Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin/LMWH, and the rate of bleeding in these patients was similar to the overall results.

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

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

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

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

Type of bleeding	PLAVIX (+ aspirin) (N=22951)		Placebo (+ aspirin) (N=22931)		P-value
	n	%	n	%	
Major* noncerebral or cerebral bleeding**	134 (0.6%)	125 (0.5%)	83 (0.4%)	0.59	
Major noncerebral	82 (0.4%)	73 (0.3%)	0.48		
Fatal	36 (0.2%)	37 (0.2%)	0.90		
Hemorrhagic stroke	55 (0.2%)	56 (0.2%)	0.91		
Fatal	39 (0.2%)	41 (0.2%)	0.81		
Other noncerebral bleeding (non-major)	831 (3.6%)	721 (3.1%)	0.005		
Any noncerebral bleeding	896 (3.9%)	777 (3.4%)	0.004		

* Major bleeds are cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.

** The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for PLAVIX + aspirin by age were: <60 years = 0.3%, ≥60 to <70 years = 0.7%, ≥70 years 0.8%. Event rates for placebo + aspirin by age were: <60 years = 0.4%, ≥60 to <70 years = 0.6%, ≥70 years 0.7%.

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

Table 7: Adverse Events Occurring in $\geq 2.5\%$ of PLAVIX Patients in CAPRIE

Body System Event	% Incidence (% Discontinuation)	
	PLAVIX (n=9599)	Aspirin (n=9586)
<i>Body as a Whole - general disorders</i>		
Chest Pain	8.3 (0.2)	8.3 (0.3)
Accidental/Infllicted 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)
<i>Cardiovascular disorders, general</i>		
Edema	4.1 (<0.1)	4.5 (<0.1)
Hypertension	4.3 (<0.1)	5.1 (<0.1)
<i>Central & peripheral nervous system disorders</i>		
Headache	7.6 (0.3)	7.2 (0.2)
Dizziness	6.2 (0.2)	6.7 (0.3)
<i>Gastrointestinal system disorders</i>		
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)
<i>Metabolic & nutritional disorders</i>		
Hypercholesterolemia	4.0 (0.1)	4.4 (<0.1)
<i>Musculo-skeletal system disorders</i>		
Arthralgia	6.3 (0.1)	6.2 (0.1)
Back Pain	5.8 (0.1)	5.3 (<0.1)
<i>Platelet, bleeding, & clotting disorders</i>		
Purpura/bruise	5.3 (0.3)	3.7 (0.1)
Epistaxis	2.9 (0.2)	2.5 (0.1)
<i>Psychiatric disorders</i>		
Depression	3.6 (0.1)	3.9 (0.2)
<i>Respiratory system disorders</i>		
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 (0.1)
Coughing	3.1 (<0.1)	2.7 (<0.1)
<i>Skin & appendage disorders</i>		
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)
<i>Urinary system disorders</i>		
Urinary tract infection	3.1 (0)	3.5 (0.1)

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

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

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

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

Body as a whole: Allergic reaction, necrosis ischemic. **Cardiovascular disorders:** Edema generalized. **Gastrointestinal system disorders:** Peptic, gastric or duodenal ulcer, gastritis, gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic. **Liver and Biliary system disorders:** Bilirubinemia, hepatitis infectious, liver fatty. **Platelet, bleeding and clotting disorders:** hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia. **Red blood cell disorders:** Anemia aplastic, anemia hypochromic. **Reproductive disorders, female:** Menorrhagia. **Respiratory system disorders:** Hemothorax. **Skin and appendage disorders:** Bullous eruption, rash erythematous, rash maculopapular, urticaria. **Urinary system disorders:** Abnormal renal function, acute renal failure. **White cell and reticuloendothelial system disorders:** Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutropenia.

Postmarketing Experience

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

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

OVERDOSAGE

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

Recommendations About Specific Treatment:

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

DOSAGE AND ADMINISTRATION

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

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

Acute Coronary Syndrome

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

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

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

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