For the use only of a Registered Medical Practitioner

CERUVIN

(Clopidogrel bisulfate tablets)

COMPOSITION

CERUVIN

Each film-coated tablet contains:

Clopidogrel bisulfate

equivalent to Clopidogrel .....75 mg

DESCRIPTION[1]

CERUVIN (clopidogrel bisulfate tablets) is an inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation acting by direct inhibition of ADP binding to its receptor and of the subsequent ADP mediated activation of the glycoprotein GP IIb/ IIIa complex. It is chemically designated as 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.

PHARMACOLOGY[1,2]

- **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 cardiovascular 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.
- **Pharmacokinetics:** 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 clopidogrel 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 □g/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.

Pharmacokinetics in special population

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 clopidogrel 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 clopidogrel per day.

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.

INDICATIONS[1,2]

CERUVIN (clopidogrel bisulfate tablets) 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, clopidogrel 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 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, clopidogrel 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, **CERUVIN** (clopidogrel bisulfate tablets) 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.

DOSAGE AND ADMINISTRATION[1,2]

- ***Recent MI, Recent Stroke, or Established Peripheral Arterial Disease:*** The recommended daily dose of **CERUVIN** (clopidogrel bisulfate tablets) is 75 mg once daily.
- ***Acute Coronary Syndrome :*** For patients with non- ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI), **CERUVIN** (clopidogrel bisulfate tablets) should be initiated with a single 300 mg (four tablets) 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 **CERUVIN** (clopidogrel bisulfate tablets). In Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events study, most patients with Acute Coronary Syndrome also received heparin acutely.

For patients with ST-segment elevation acute myocardial infarction, the recommended dose of **CERUVIN** (clopidogrel bisulfate tablets) is 75 mg once daily, administered in combination with aspirin, with or without thrombolytics. **CERUVIN** (clopidogrel bisulfate tablets) may be initiated with or without a loading dose

CERUVIN (clopidogrel bisulfate tablets) can be administered with or without food.

No dosage adjustment is necessary for elderly patients or patients with renal disease.

PRECAUTIONS[1,2]

- **General:** Clopidogrel 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) and in patients receiving treatment with ASA, non-steroidal anti-inflammatory drugs, heparin, glycoprotein IIb/IIIa inhibitors or thrombolytics. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with warfarin is not recommended since it may increase the intensity of bleedings.

If a patient is to undergo elective surgery and an antiplatelet effect is not desired, clopidogrel should be discontinued 7 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 **ADVERSE REACTIONS**).

In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and clopidogrel has not been shown to be more effective than clopidogrel alone, but the combination has been shown to increase major bleeding.

Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with Acetyl Salicylic Acid [ASA]), and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentist that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken.

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterized by thrombocytopenia and microangiopathic hemolytic anemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

In view of the lack of data, in patients with acute myocardial infarction with ST-segment elevation, clopidogrel therapy should not be initiated within the first few days following myocardial infarction.

In view of the lack of data, clopidogrel cannot be recommended in acute ischemic stroke (less than 7 days).

GI Bleeding: In CAPRIE study (clopidogrel + aspirin), clopidogrel was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. In CURE (Placebo + aspirin), the incidence of major gastrointestinal bleeding was 1.3% vs. 0.7% (Clopidogrel + aspirin vs. placebo + aspirin, respectively). Clopidogrel 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 clopidogrel bisulfate.

Hepatic Insufficiency: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Clopidogrel bisulfate should be used with caution in this population.

Renal Insufficiency: Experience is limited in patients with severe renal impairment. Clopidogrel bisulfate should be used with caution in this population.

- **Information for patients:** Patients should be told that they may bleed more easily and it may take them longer than usual to stop bleeding when they take clopidogrel or clopidogrel combined with aspirin, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking clopidogrel and/or any other product known to affect bleeding before any surgery is scheduled & before any new drug is taken.
- **Contraindications:** The use of **CERUVIN** (clopidogrel bisulfate tablets) 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.
  - Severe liver impairment.
  - Breast feeding
- **Pregnancy:** ***Pregnancy Category B***. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m^2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel should be used during pregnancy only if clearly needed.
- **Lactation:** 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.
- **Pediatrics:** Safety and effectiveness in the pediatric population have not been established.
- **Geriatrics:** Of the total number of subjects in controlled clinical studies, approximately 50% of patients treated with clopidogrel were 65 years of age and over. Approximately 16% of patients treated with clopidogrel were 75 years of age and over.
- **Drug Interactions:** *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 clopidogrel. Clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregation. Clopidogrel and aspirin have been administered together for up to one year.

Heparin: In a study in healthy volunteers, clopidogrel 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 clopidogrel.

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

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken with caution (see **PRECAUTIONSGeneral**).

Thrombolytics: The safety of the concomitant administration of clopidogrel, recombinant tissue plasminogen activator (rt-PA) and heparin was assessed in patients with recent myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when rt-PA and **heparin are coadministered with ASA. The safety of the concomitant administration of clopidogrel with other** thrombolytic agents has not been formally established and should be undertaken with caution.

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors.

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when clopidogrel was coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of clopidogrel 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 clopidogrel.

At high concentrations *in vitro*, clopidogrel inhibits P_{450} (2C9). Accordingly, clopidogrel 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 clopidogrel.

In addition to the above specific interaction studies, patients enrolled in clinical trials with clopidogrel 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 had not 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 is no data on their concomitant use with clopidogrel.

Drug/Laboratory Test Interactions : None known

- **Carcinogenicity /Mutagenicity /Impairment of Fertility:** There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg.

Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice).

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m^2 basis).

- **Warnings:** *Thrombotic thrombocytopenic purpura (TTP):* TTP has been reported rarely following use of clopidogrel, sometimes after a short exposure (<2 weeks). TTP is a serious condition and requires urgent referral to a hematologist for 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 world-wide postmarketing experience, however, TTP has been reported at a rate of about four cases per million patients exposed, or about 11 cases per million patient-years. The background rate is thought to be about four cases per million person-years **(see ADVERSE REACTIONS).**

ADVERSE REACTIONS[1,2]

Clopidogrel 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 clopidogrel 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 clopidogrel, 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 clopidogrel compared to 0.5% for aspirin.

In CURE, clopidogrel use with aspirin was associated with an increase in bleeding compared to placebo with aspirin (see Table 1). There was an excess in major bleeding in patients receiving clopidogrel 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 1 for patients receiving both clopidogrel and aspirin in CURE.

Table 1: CURE Incidence of bleeding complications (% patients)

Event	(+ aspirin)* (n=6259)	(+ 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 clopidogrel + aspirin was dose-Dependent on aspirin: <100 mg=2.6%; 100-200 mg= 3.5%; >200 mg=4.9%

Major bleeding event rates for clopidogrel + 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% clopidogrel + 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 clopidogrel + 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 clopidogrel + 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 clopidogrel + 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 2 below.

Table 2: Number (%) of Patients with Bleeding Events in COMMIT

Type of bleeding	Clopidogrel (+ aspirin) (N=22961)	Placebo (+ aspirin) (N=22891)	P-value
Major* noncerebral or cerebral bleeding**	134 (0.6%)	125 (0.5%)	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 clopidogrel + 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 ≥ 2.5% of patients on clopidogrel in the CAPRIE controlled clinical trials are shown below regardless of relationship to clopidogrel. The median duration of therapy was 20 months, with a maxim of 3 years.

Table 3: Adverse Events Occurring in ≥ 2.5% of Clopidogrel Patients in CAPRIE

	% Incidence (% Discontinuation)	
Body System Event	Clopidogrel [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 respiratory 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 clopidogrel bisulfate in the controlled clinical trials are listed below regardless of relationship to clopidogrel. 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 clopidogrel in the controlled clinical trials are listed below regardless of relationship to clopidogrel. 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, 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*: - myalgia

OVERDOSAGE[1,2]

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 hemorrhage in all species.

Recommendations about Specific Treatment: No antidote to the pharmacological activity of clopidogrel has been found. Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of clopidogrel if quick reversal is required.

STORAGE

Store below 25°C, protected from moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

SUPPLY

Blister strip of 10 tablets

REFERENCES

1. Prescribing information of *PLAVIX*® Tablets, Sanofi-Synthelabo, Bristol-Myers Squibb Company, USA. February 2007.
2. ABPI Compendium of Data Sheets and Summaries of Product Characteristics, *PLAVIX*, Bristol-Myers Squibb Pharmaceuticals Ltd. September 2006.

Information Compiled in July 2007

MADE IN INDIA

RANBAXY

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