Clopido

(Clopidogrel)

کلوپیڈو

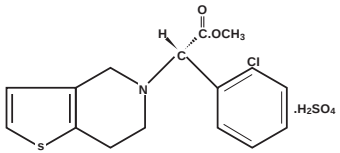
(کلوپیڈوگرل)

75mg Tablets

75 ملی گرام گولیاں

Each film coated tablet contains:
Clopidogrel bisulfate (U.S.P.) equivalent to Clopidogrel 75mg
Product Complies USP Specs.

DESCRIPTION
CLOPIDO (clopidogrel bisulphate) is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Chemically it is methyl (+)-(S)-α-(2-chlorophenyt)-6,7 dihydrothieno[3,2-c] pyrldine-5(*4H*)-acetate sulphate (1:1). The empirical formula of clopidogrel bisulphate is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ and its molecular weight is 419.9. The structural formula is as follows:



CLOPIDO for oral administration is provided as film-coated tablets containing 97.875mg of clopidogrel bisulphate which is the molar equivalent of 75 mg of clopidogrel base.

CLINICAL PHARMACOLOGY
Mechanism of Action
Clopidogrel is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established atherosclerotic cardiovascular disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, or need for bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate.

Pharmacodynamic Properties
Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel. Repeated doses of 75mg clopidogrel per day inhibit ADP induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg clopidogrel per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Pharmacokinetics
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 add derivative, and it too has no effect on platelet aggregation. It represents about 85% of the circulating drug related compounds in plasma.

Following an oral dose of ^{14}C- labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half- life of the main circulating metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days.

Effect of Food: Administration of CLOPIDO (clopidogrel bisulphate) 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 150mg 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 100mg/mL.

Metabolism and Elimination: in vitro and in vivo, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

Special Populations
Geriatric Patients: Plasma concentrations of the main circulating metabolite are significantly higher in elderly (≥75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients: After repeated doses of 75mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15mL/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 lime was similar to healthy volunteers receiving 75mg of clopidogrel per day. No dosage adjustment is needed in renally impaired patients.

Gender: No significant difference was observed in the plasma levels of the main circulating metabolite between males and females. In a small study comparing men and women, less inhibition of ADP induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events and abnormal clinical laboratory parameters was similar in men and women.

Race: Pharmacokinetic differences due to race have not been studied.

INDICATIONS AND USAGE
CLOPIDO (clopidogrel bisulphate) is indicated for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease.

CONTRAINDICATIONS

The use of CLOPIDO 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.

WARNING
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 requiring prompt treatment. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. TTP was not seen during clopidogrel's clinical trials, which included over 11,300 clopidogrel-treated patients. In world-wide post marketing experience, however, TTP has been reported at a rate of about four cases per million patients exposed, or about 11 cases per million patient-years. The background rate is thought to be about four cases per million person-years.

PRECAUTIONS
General
As with other anti-platelet agents, CLOPIDO should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions. If a patient is to undergo elective surgery and an antiplatelet effect is not desired. CLOPIDO should be discontinued 7 days prior to surgery.

GI Bleeding: CLOPIDO prolongs the bleeding time. In CAPRIE, Clopidogrel was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. CLOPIDO should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions (such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) should be used with caution in patients taking CLOPIDO.

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

Information for Patients
Patients should be told that it may take them longer than usual to stop bleeding when they take CLOPIDO, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking CLOPIDO 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 500mg of aspirin twice a day for I day did not significantly increase the prolongation of bleeding time induced by clopidogrel. Clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregation. The safety of chronic concomitant administration of aspirin and clopidogrel has not been established.

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. The safety of this combination has not been established, however, and concomitant use should be undertaken with caution.

Non-Steroidal 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: The safety of the coadministration of clopidogrel with warfarin has not been established. Consequently, concomitant administration of these two agents should be undertaken with caution. (See PrecautionsGeneral).

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 bisulphate.
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 nonsteroidal 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 entered into CAPRIE received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents, antiepileptic agents and hormone replacement therapy without evidence of clinically significant adverse interactions.

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 upto 77 mg/kg per day, which afforded plasma

D1B

Platinum
Pharmaceuticals (Pvt.) Ltd.

Product : Clopido Tablet
Components: Leaflet (TP)
Country : Local (Pakistan)
Dimension: 85 mm x 145 mm (255mm x 145 mm)
Started Date : 10-03-2017
Modified Date: 13-03-2017
Concepts by : Nadeem ul Haq
Design by : Rahil Rahim
QAR No. AW17-0211
Supersedes: 09057-0407

COLORS : PANTONE SOLID COATED
Pantone Black C

Department	Marketing	Regulatory	Qulity Control	Quality Control Head	Procurement
Remarks					
Signature					
Date / Time					

exposures >25 times that in humans at the recommended daily dose of 75mg.

Clopidogrel was not genetoxic 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 upto 400 mg/kg per day (52 times the recommended human dose on a mg/m$_2$ basis).

Pregnancy
Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses upto 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, CLOPIDO should be used during pregnancy only if clearly needed.

Nursing Mothers
Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

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

ADVERSE REACTIONS
Clopidogrel has been evaluated for safety in more than 11,300 patients, including over 7,000 patients treated for 1 year or more. The overall tolerability of clopidogrel was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. The clinically important adverse events observed in CAPRIE are discussed below.

Hemorrhagic: In patients receiving clopidogrel in CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2.0%. 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.

Neutropenial/agranulocytosis: Ticlopidine, a drug chemically similar to clopidogrel, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/mL). Patients in CAPRIE (see Clinical Trials) were intensively monitored for neutropenia. Severe neutropenia was observed in six patients, four on clopidogrel and two on aspirin. Two of the 9599 patients who received clopidogrel and none of the 9586 patients who received aspirin had neutrophil counts of zero. One of the four clopidogrel patients was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with clopidogrel.
Although the risk of myelotoxicity with clopidogrel thus appears to be quite low, this possibility should be considered when a patient receiving clopidogrel demonstrates fever or other sign of infection.

Gastrointestinal: Overall, the incidence of gastrointestinal events (e.g., abdominal pain, dyspepsia, gastritis and constipation) in patients receiving clopidogrel bisulphate was 27.1%, compared to 29.8% in those receiving aspirin. The incidence of peptic, gastric or duodenal ulcers was 0.7% for clopidogrel and 1.2% for aspirin.

Cases of diarrhea were reported in 4.5% of patients in the clopidogrel group compared to 3.4% in the aspirin group. However, these were rarely severe (clopidogrel=0.2% and aspirin=0.1 %).

The incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for clopidogrel and 4.0% for aspirin.

Rash and Other Skin Disorders: The incidence of skin and appendage disorders in patients receiving clopidogrel was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious).

The overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for clopidogrel and 0.8% for aspirin. adverse events occurring in ≥2.5% of patients on clopidogrel in the CAPRIE controlled clinical trial are shown below regardless of relationship to clopidogrel. The median duration of therapy was 20 months, with a maximum of 3 years.
Adverse Events occurring in ≥2.5% of Clopidogrel patients % incidencs (% discontinuation).

BODY EVENTS OCCURRING EVENT	Clopidogrel [n=9599]	Aspirin [n=9586]
Body as a Whole-general disorders		
Chest Pain	8.3 (0.2)	8.3 (0.3)
Accidental 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)
Dininess	6.2 (0.2)	6.7 (0.3)
GastroIntestinal system disorders		
Abdominal Pain	5.6 (0.7)	7.1 (1.0)
Dyspepsia	5.2 (0.6)	6.1 (0.7)
Diarrhea	4.5 (0.4)	3.4 (0.3)
Nausea	3.4 (0.5)	3.8 (0.4)
Metabolic & nutritional disorders		
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)
Musculo-skeletal system disorders		
Arthralgia	6.3 (0.1)	6.2 (0.1)
Back pain	5.8 (0.1)	5.3 (<0.1)
Platelet, bleeding, & clotting disorders		
Purpura	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		
Rash	4.2 (0.5)	3.5 (0.2)
Pruritus	3.3 (0.3)	1.6 (0.1)
Urinary system disorders		
Urinary tract infection	3.1 (0)	3.5 (0.1)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Other adverse experience of potential importance occurring in 1% to 2.5% of patients receiving clopidogrel bisulphate in the CAPRIE controlled clinical trial are listed below regardless of relationship to clopidogrel. In general, the incidence of these events was similar in the aspirin-treated group.

Autonomic Nervous System Disorders: Syncope, Palpitation.
Body as a Whole - General Disorders: Asthenia, 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 are listed below regardless of relationship to clopidogrel. In general, the incidence of these events was similar in the aspirin group.

Body as a Whole: Allergic reaction, necrosis ischemic.
Cardiovascular Disorders: Edema generalized.
Gastrointestinal System Disorders: Gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic.
Liver and Biliary System Disorders: Bilirubinemia, hepatitis infectious, liver fatty.
Platelet, Bleeding and Clotting Disorders: Hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage. pulmonary hemorrhage, purpura allergic, thrombocytopenia.
Red Blood Cell Disorders: Anemia aplastic, anemia hypochromic.
Reproductive Disorders-Female: Menorrhagia.
Respiratory System Disorders: Hemothorax.
Skin and Appendage Disorders: Bullous eruption, rash erythematous. rash maculopapular, urticaria.
White Cell and *Reticuloendothelial System Disorders:* Agranulocytosis, granulocytopenia, leukemia, leucopenia, neutrophils decreased.

Postmarketing Experience
The following events have been reported spontaneously from worldwide postmarketing experience: very rare cases of hypersensitivity reactions including angioedema, bronchospasms, and anaphylactoid reactions. Suspected thrombotichthrombocytopenia purpura (TTP) has been reported as part of the woldwide postmarketing experience, see **WARNINGS.**

OVERDOSAGE
One case of deliberate overdosage with clopidogrel was reported in the large, controlled clinical study. A 34-year-Old woman took a single 1,050mg dose of clopidogrel (equivalent to 14 standard 75mg tablets). There were no associated adverse events. No special therapy was instituted, and she recovered without sequelae.

No adverse events were reported after single oral administration of 600 mg (equivalent to 8 standard 75mg tablets) of clopidogrel in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75mg of clopidogrel per day.

A single oral dose of clopidogrel at 1500 or 2000 mg/kg lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.

Recommendations About Specific Treatment: Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of clopidogrel if quick reversal is required.

DOSAGE AND ADMINISTRATION
The recommended dose of CLOPIDO one tablet daily with or without food. No dosage adjustment is necessary for elderly patients or patients with renal disease.

HOW SUPPLIED
CLOPIDO (Clopidogrel) tablets are available in Alu Alu Blister pack of 10's.

STORAGE
Store below 30°C in a dry place, protect from light.
To be dispensed on the prescription of a registered medical practitioner only.
Keep out of the reach of children.

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Platinum Pharmaceuticals (Pvt.) Ltd.
A 20,North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

QAR No. AW17-0211

D1B

Platinum Pharmaceuticals (Pvt.) Ltd.

Product : Clopido Tablet
Components: Leaflet (TP)
Country : Local (Pakistan)
Dimension: 85 mm x 145 mm (255mm x 145 mm)
Started Date : 10-03-2017
Modified Date: 13-03-2017
Concepts by : Nadeem ul Haq
Design by : Rahil Rahim
QAR No. AW17-0211
Supersedes: 09057-0407

COLORS : PANTONE SOLID COATED
Pantone Black C

Department	Marketing	Regulatory	Qulity Control	Quality Control Head	Procurement
Remarks					
Signature					
Date / Time					