

# CLOPIDOGREL

## PLATZ

75 mg

Film-Coated Tablet  
ANTITHROMBOTIC



### FORMULATION:

Each film-coated tablet contains:  
Clopidogrel (As bisulfate) USP  
Eq. to Clopidogrel ..... 75 mg

### PRODUCT DESCRIPTION:

Reddish brown coloured, round shaped, biconvex both side plain film-coated tablet.

### CLINICAL PHARMACOLOGY:

#### Mechanism of Action and Pharmacodynamic Properties

Clopidogrel is a prodrug, one of whose metabolites 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 platelet function can reduce the event rate.

Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y<sub>12</sub> receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Consequently, platelets exposed to Clopidogrel's active metabolite are affected for the remainder of their lifespan (about 7 to 10 days). Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other drugs, not all patients will have adequate platelet inhibition.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Clopidogrel. Repeated doses of 75 mg 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 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:

**Absorption:** After single and repeated oral doses of 75 mg per day, Clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged Clopidogrel (approximately 2.2-2.5 ng/mL after a single 75mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of Clopidogrel metabolites.

**Effect of Food:** The effect of food on the bioavailability of the parent compound or active metabolite is currently not known.

**Distribution:** Clopidogrel and the main circulating inactive 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 mcg/mL.

**Metabolism:** Clopidogrel is extensively metabolized by the liver. *In vitro* and *in vivo*, Clopidogrel is metabolized according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Cytochromes first oxidize Clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of Clopidogrel. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

**Elimination:** Following an oral dose of <sup>14</sup>C-labeled Clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post dosing. After a single oral dose of 75 mg, Clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the inactive acid 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. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

### INDICATION:

Used as prophylaxis for thromboembolic events, and for the treatment of acute coronary syndromes including unstable angina and non-Q wave myocardial infarction.

### DOSAGE AND ADMINISTRATION:

Prophylaxis of thromboembolic events- the usual dose is 75 mg once daily.

Management of acute coronary syndromes, unstable angina and non-Q wave myocardial infarction- 300 mg loading dose, followed by 75 mg once daily.

Or as prescribed by the physician.

### CONTRAINDICATIONS:

Clopidogrel is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients in the formulation. Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

### WARNINGS:

Reduced effectiveness due to impaired CYP2C19 function:

The inhibition of platelet aggregation by Clopidogrel is entirely due to an active metabolite. Clopidogrel is metabolized to this active metabolite in part by CYP2C19. This metabolism can be impaired by genetic variations in CYP2C19 and by concomitant medications that interfere with CYP2C19. Avoid use of Clopidogrel in patients with impaired CYP2C19 function due to known genetic variation or due to drugs that inhibit CYP2C19 activity.

**Genetic variations:** Patients with genetically reduced CYP2C19 function have diminished antiplatelet responses and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function.

**Drug interactions:** Co-administration of Clopidogrel with Omeprazole, a proton pump inhibitor that is an inhibitor of CYP2C19, reduces the pharmacological activity if given concomitantly or if given 12 hours apart. There is no evidence that other drugs that reduce stomach acid, such as most H<sub>2</sub> blockers (except Cimetidine, which is a CYP2C19 inhibitor) or antacids interfere with the antiplatelet activity of Clopidogrel.

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 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.

### PRECAUTIONS:

General: 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, it should be discontinued 5 days prior to surgery.

Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment.

In patients with recent TIA or stroke who are at high risk of 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.

**GI Bleeding:** In CAPRIE, it 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% (Clopidogrel + Aspirin vs. placebo + Aspirin, respectively). It 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.

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

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

Information for Patients

Patients should be told that while taking or combined with Aspirin:

- it may take them longer than usual to stop bleeding;
- they may bruise and/or bleed more easily;
- they should report any unusual bleeding to their physician;
- they should tell their physician about any other medications they are taking, including prescription or over-the-counter Omeprazole;
- they should inform physicians and dentists that they are taking Aspirin or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.

### DRUG INTERACTIONS:

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of Clopidogrel and a reduction in platelet inhibition. Avoid concomitant use of drugs that inhibit CYP2C19, including Omeprazole, Esomeprazole, Cimetidine, Fluconazole, Ketoconazole, Voriconazole, Etravirine, Felbamate, Fluoxetine, Fluvoxamine, and Ticlopidine.

Studies of specific drug interactions yielded the following results:

**Omeprazole:** In a crossover clinical study, 72 healthy subjects were administered with Clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with Omeprazole (80 mg at the same time as) for 5 days. The exposure to the active metabolite of Clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when Clopidogrel and Omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47% (24 hours) and 30% (Day 5) when Clopidogrel were administered together with Omeprazole. In another study, 72 healthy subjects were given the same doses of Clopidogrel and Omeprazole but the drugs were administered 12 hours apart; in take the result were similar indicating that administering Clopidogrel and Omeprazole at different times does not prevent their interaction.

**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. Co-administration 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 with Clopidogrel was associated with increased occult gastrointestinal blood loss. NSAIDs and Clopidogrel should be co-administered with caution.

**Warfarin:** Because of the increased risk of bleeding, the concomitant administration of Warfarin with Clopidogrel should be undertaken with caution.

**Other Concomitant Therapy:** No clinically significant pharmacodynamic interactions were observed when Clopidogrel was co-administered with Atenolol, Nifedipine, or both Atenolol and Nifedipine. The pharmacodynamic activity of Clopidogrel was also not significantly influenced by the co-administration of Phenobarbital or Estrogen.

The pharmacokinetics of Digoxin or Theophylline were not modified by the co-administration of Clopidogrel bisulfate.

At high concentrations *in vitro*, Clopidogrel inhibits P450 (2C9). Accordingly, it 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 co-administered with Clopidogrel.

In addition to the above specific interaction studies, patients entered into 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), 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 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<sup>2</sup> basis).

### Pregnancy:

Pregnancy Category B. Reproductive 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<sup>2</sup> 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 reproductive studies are not always predictive of a human response, 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 Clopidogrel were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with Clopidogrel were 60 years and older, 26% of whom were 70 years and older.

### ADVERSE EFFECTS:

Gastrointestinal disturbance, skin rashes, blood dyscrasias including neutropenia and thrombocytopenic purpura, haemorrhagic disorders, hepatitis, and cholestatic jaundice.

### DRUG INTERACTIONS:

Aspirin: Potentiated the effect of Aspirin on collagen-induced platelet aggregation.

NSAID: Risk of increased occult gastrointestinal blood loss.

Phenytoin, Tamoxifen, Tolbutamide, Warfarin, Torsemide, Fluvastatin: Since Clopidogrel inhibits CYP4502c9, it may interfere with the metabolism of these drugs.

### OVERDOSAGE:

Overdose following Clopidogrel administration, may lead to prolonged bleeding time and subsequent bleeding complications. A single oral dose of Clopidogrel at 1500 mg 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, difficulty in 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.

### CAUTION:

Foods, Drugs, Devices, and Cosmetics prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: [www.fda.gov.ph](http://www.fda.gov/ph).

Seek medical attention immediately at the first sign of any adverse drug reaction.

### STORAGE CONDITION:

Store at temperatures not exceeding 30°C.

### KEEP ALL MEDICINES OUT OF CHILDREN'S REACH.

### AVAILABILITY:

Alu/Alu Blister Pack x 10's (Box of 100's).

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