ABRIDGED PRODUCT INFORMATION

Product: Clopidogrel bisulfate (Plavix) 75 mg Film-Coated Tablet
Presentation: Alu-Alu blister pack x 14's (Box of 14's)
I: *Secondary prevention of atherothrombotic events* – (a) for patients with a history of recent myocardial infarction (MI), recent stroke or established peripheral arterial disease; (b) for patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave myocardial infarction [MI]) and for patients with ST-segment elevation acute myocardial infarction. *In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS)* - Clopidogrel in combination with ASA is indicated in adult patients with moderate to high-risk TIA (ABCD2[1] score ≥4) or minor IS (NIHSS[2] ≤3) within 24 hours of either the TIA or IS event. *Prevention of atherothrombotic and thromboembolic events* – (a) in patients with atrial fibrillation (AF) at increased risk of vascular events who can take vitamin K antagonist (VKA) therapy; (b) in patients with atrial fibrillation who have at least one risk factor for vascular events and who cannot take VKA therapy (e.g., specific risk of bleeding, physician assessment that patient is unable to comply with INR [International normalized ratio] monitoring or that VKA use is inappropriate)
D: *Adults & Elderly* - Clopidogrel should be given as a single daily dose of 75mg. It may be given with or without food.
C: Hypersensitivity to the drug substance or any component of the product. Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.
P: Risk of bleeding and hematological undesirable effects. Recent ischemic stroke. Thrombotic Thrombocytopenic Purpura (TTP). Acquired hemophilia. Cytochrome P450 2C19 (CYP2C19). CYP2C8 substrates. Cross-reactivity among thienopyridines. Renal and hepatic impairment.
Interactions: Drugs associated with bleeding risk. Thrombolytics. Heparin. Glycoprotein IIb/IIIa inhibitors. Injectable and Oral anticoagulants. Acetylsalicylic acid. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Selective Serotonin Reuptake Inhibitors (SSRIs). Inducers and inhibitors of CYP2C19. Proton Pump Inhibitors (PPI). Boosted anti-retroviral therapy (ART). CYP2C8 substrate drugs. Rosuvastatin.
AE: dyspepsia, abdominal pain, diarrhoea, headache, dizziness, paraesthesia, bleeding time increased, platelets decreased, nausea, gastritis, flatulence, constipation, vomiting, gastric ulcer, duodenal ulcer, rash, pruritus, leucopenia, neutrophils decreased, eosinophilia.
PD: Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel, metabolised by CYP450 enzymes, produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. 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 medicinal products, not all patients will have adequate platelet inhibition.
Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached 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 returned to baseline values, generally within 5 days after treatment was discontinued.
PK: *Absorption* - After single and repeated oral doses of 75 mg/day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/mL after a single 75-mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.
Distribution - Clopidogrel and the main circulating (inactive) metabolite bind reversibly in vitro to human plasma proteins (98% and 94%, respectively). The binding is non-saturable in vitro up to a concentration of 100 mg/L.
Metabolism – Clopidogrel is extensively metabolised by the liver. In vitro and in vivo, clopidogrel is metabolised 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. Clopidogrel is first metabolised 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. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. The Cmax of the active metabolite is twice as high following a single 300-mg clopidogrel loading dose as it is after four days of 75-mg maintenance dose. Cmax occurs approximately 30 to 60 minutes after dosing.
Elimination - Following an oral dose of 14C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

SmPC based on CCDSv29-30
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[1] Age, Blood pressure, Clinical features, Duration, and Diabetes mellitus diagnosis
[2] National Institutes of Health Stroke Scale