Clopidogrel

Plogrel®

75mg Film-Coated Tablet

Antithrombotic

FORMULATION
Each film-coated tablet contains:
Clopidogrel (as bisulfate).....75mg

PRODUCT DESCRIPTION
Clopidogrel (Plogrel®) 75 mg film-coated tablet- pink colored, circular, biconvex, film-coated tablet.

PHARMACODYNAMICS / MECHANISM OF ACTION
Clopidogrel is an irreversible inhibitor of platelet aggregation. It acts by irreversibly modifying the platelet adenosine 5'- diphosphate (ADP) receptor, thus selectively inhibiting the binding of ADP to its platelet receptor and the subsequent activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan. Biotransformation of clopidogrel to its active metabolite is necessary to produce inhibition of platelet aggregation.

PHARMACOKINETICS
Clopidogrel is rapidly but incompletely absorbed after oral doses; absorption appears to be at least 50%. It is a prodrug and is extensively metabolized in the liver, mainly to the inactive carboxylic acid derivative; metabolism is mediated by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6, and to a lesser extent by CYP1A2, CYP1A1, and CYP2C19. The active metabolite appears to be a thiol derivative but has not been identified in plasma.

Clopidogrel and the carboxylic acid derivative are highly protein bound. Clopidogrel and its metabolites are excreted in urine and in feces; about 50% of an oral dose is recovered from the urine and about 46% from the feces.

INDICATIONS
For prevention of atherosclerotic events in patients with:
- History of recent myocardial infarction (within a few days until less than 35 days from occurrence), recent ischemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease
- Non-ST segment elevation acute coronary syndrome (unstable angina / non-Q-wave MI) including patients who are managed medically with percutaneous coronary intervention (with or without stent) or coronary artery bypass graft (CABG)

It is given prophylactically as an alternative to aspirin in patients at risk of thromboembolic disorders such as myocardial infarction, peripheral arterial disease and stroke.

DOSAGE AND ADMINISTRATION
Recent MI or stroke, or established peripheral arterial disease
Recommended Dose: Orally, 75 mg once daily with or without food
Prophylaxis of thromboembolic events
Usual Dose: Orally, 75mg once daily
Non-ST segment elevation acute coronary syndrome (unstable angina / non-Q-wave MI)
-Initiate a single 300 mg loading dose and then continue at 75 mg once daily in combination with aspirin
-A higher bleeding risk was associated with combined use of clopidogrel and aspirin. It is recommended that physicians monitor their patients through clinical and laboratory evaluation.

Or as prescribed by a physician

CONTRAINDICATIONS
- Known hypersensitivity to clopidogrel or any component in the formulation
- Presence of active pathological bleeding (e.g., peptic ulcer, intracranial hemorrhage) or coagulation disorders

WARNINGS AND PRECAUTIONS
- Cases of thrombocytopenic purpura (usually occurring within the first 2 weeks of therapy) have been reported; urgent plasmapheresis is required.
- Use with caution in patients with platelet disorders and/or at increased risk for bleeding (e.g., peptic ulcer disease, trauma, or surgery), severe hepatic and renal impairment
- Consider discontinuing clopidogrel 5 days prior to elective surgery, except in patients with cardiac stents that have not completed their full course of dual antiplatelet therapy. Patient-specific situations need to be discussed with a physician or cardiologist.

DRUG INTERACTIONS
Aspirin - Clopidogrel may potentiate aspirin's antithrombotic effects resulting in increased risk of bleeding.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) [e.g., Naproxen, Ibuprofen, Diclofenac] - Increased occult GI blood loss has also been reported in concomitant use with NSAIDs. Co-administer with caution.

Anticoagulants - Concomitant use of clopidogrel with anticoagulants (e.g., warfarin, argatroban, enoxaparin, bivalirudin, heparin) may cause increased risk of bleeding.

Drugs Metabolized by CYP2C9 Isoenzyme - Clopidogrel may inhibit the cytochrome P450 isoenzyme CYP2C9 and interactions with drugs metabolized by this isoenzyme (e.g., phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and NSAIDs) are possible.

Bupropion - Clopidogrel has been found to reduce the conversion of bupropion to its active metabolite suggesting that clopidogrel inhibits cytochrome P450 isoenzyme CYP2B6.

Statins and Ciclosporin - Rhabdomyolysis has been reported to develop in patients administered with clopidogrel in addition to ciclosporin and a statin (e.g., atorvastatin, lovastatin or simvastatin). It has been suggested that the mechanism is a three-way interaction involving competition for binding sites on cytochrome P450 isoenzyme CYP3A4 between statins and clopidogrel, exacerbated by ciclosporin-mediated enzyme inhibition.

Macrolide Antibiotics - CYP3A4-inhibiting macrolides (e.g., clarithromycin, erythromycin and troleandomycin) may attenuate the effects of clopidogrel.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

- **Pregnancy and Lactation**

  Pregnancy Category B. Teratogenic effects were not observed in animal studies. There are, however, no adequate and well controlled studies in pregnant women. Use in pregnancy only if clearly needed.

  Clopidogrel is distributed into milk in rats. It is not known whether the drug is distributed into milk in humans. Discontinue breastfeeding or the drug because of potential adverse effects in infants.

- **Children**

  Safety and efficacy have not been established in patients younger than 21 years old.

- **Elderly**

  Dosage adjustment based solely on age does not appear to be necessary in geriatric patients.

ADVERSE EFFECTS
As with all drugs which may affect hemostasis, bleeding is associated with clopidogrel. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the concurrent use of multiple agents which alter hemostasis and patient susceptibility. Other adverse effects are as follows:

Gastrointestinal: Abdominal pain, vomiting, nausea, dyspepsia, gastritis, diarrhea, constipation, GI hemorrhage, pancreatitis, stomatitis.
Cardiovascular: Chest pain, edema, hypertension, atrial fibrillation, cardiac failure, palpitation, syncope, angioedema, vasculitis
Central Nervous System: Headache, dizziness, depression, fatigue, general pain, fever, insomnia, vertigo, anxiety, hemorrhagic stroke, intracranial hemorrhage, confusion, hallucination
Dermatologic: Rash (severe, maculopapular), pruritus, eczema, allergic reaction, anaphylactoid reaction, bullous eruption, urticaria, erythema multiforme, lichen planus, Stevens Johnson syndrome, toxic epidermal necrolysis.
Endocrine-Metabolic: Hypercholesterolemia, gout, hyperuricemia, pancreatitis
Immunologic: Serum sickness
Genitourinary: Urinary tract infection, cystitis, hematuria
Hematologic: Bleeding, thrombotic thrombocytopenic purpura (TTP), epistaxis, hematoma, anemia, agranulocytosis, bilirubinemia, granulocytopenia, hypochromic anemia, neutropenia, leukopenia, thrombocytopenia, aplastic anemia, retroperitoneal bleeding, pancytopenia
Hepatic: Liver function test abnormalities, fatty liver, acute liver failure, hepatitis
Neuromuscular & skeletal: Arthralgia, back pain, arthritis, leg cramps, neuralgia, paresthesia, weakness
Respiratory: Dyspnea, rhinitis, bronchitis, cough, upper respiratory infection, bronchospasm, hemoptysis, hemothorax, pulmonary hemorrhage, interstitial pneumonitis
Ocular: Cataract, conjunctivitis, ocular hemorrhage
Miscellaneous: Flu-like syndrome, ischemic necrosis, menorrhagia, hypersensitivity, taste disorder

OVERDOSAGE AND MANAGEMENT
Symptoms of acute toxicity include vomiting, prostration, difficulty breathing, and gastrointestinal hemorrhage. Platelet transfusions may be an appropriate treatment when attempting to reverse the effects of clopidogrel. After decontamination, treatment is symptomatic and supportive.

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

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, report to the FDA at www.fda.gov.ph and Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

KEEP OUT OF REACH OF CHILDREN

STORE AT TEMPERATURES NOT EXCEEDING 30°C

AVAILABILITY
Clopidogrel (Plogrel®) 75 mg tablet in box of 50's
(in strip foil by 10's)

Manufactured by Ajanta Pharma Limited
Plot No. B-4/5/6, MIDC, Paithan, Aurangabad, 431148
Maharashtra State, India
Imported and Distributed by **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

Date of First Authorization: July 2009
Date of Revision: July 2009

Registration No.
Plogrel® 75mg Film-coated Tablet: DRP-3168-01

Reg. IPOPHIL

3010974
THE141402IN02