CLOPIDOGREL Bisulfate

DEPLATT
75 mg Film-Coated Tablet
Antithrombotic

FORMULATION
Each film-coated tablet contains:
Clopidogrel (as Bisulfate) ..... 75 mg
PRODUCT DESCRIPTION
Clopidogrel Bisulfate (Deplatt) 75 mg is a salmon pink coloured, round, beveled edge, biconvex film coated tablet plain on both sides.
CLINICAL PHARMACOLOGY
Mechanism of Action
Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y class of ADP receptors on platelets.
Pharmacodynamics
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 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.
Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel bisulfate. Repeated doses of 75 mg clopidogrel bisulfate 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 bisulfate 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.
Geriatric Patients
Elderly (≥75 years) and young healthy subjects had similar effects on platelet aggregation.
Renally-Impaired Patients
After repeated doses of 75 mg clopidogrel bisulfate per day, patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) and moderate renal impairment (creatinine clearance from 30 to 60 mL/min) showed low (25%) inhibition of ADP-induced platelet aggregation.
Hepatically-Impaired Patients
After repeated doses of 75 mg clopidogrel bisulfate per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects.
Gender
In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women.
Pharmacokinetics
Clopidogrel is a prodrug and is metabolized to a pharmacologically active metabolite and inactive metabolites.
Absorption
After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.
Effect of Food
Clopidogrel bisulfate can be administered with or without food. In a study in healthy male subjects when clopidogrel bisulfate 75 mg per day was given with a standard breakfast, mean inhibition of ADP induced platelet aggregation was reduced by less than 9%. The active metabolite AUC was unchanged in the presence of food, while there was a 57% decrease in active metabolite C. Similar results were observed when a clopidogrel bisulfate 300 mg loading dose was administered with a high fat breakfast.
Metabolism
Clopidogrel is extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. 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. This metabolic pathway is mediated by CYP2C19, CYP3A, CYP2B6 and CYP1A2. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.
The C 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. C occurs approximately 30 to 60 minutes after dosing. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: increasing the dose by a factor of four results in 2.0- and 2.7-fold increases in C and AUC, respectively.
Elimination
Following an oral dose of 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 half-life of the active metabolite is about 30 minutes.
INDICATIONS
Indicated for the reduction of thrombotic events in Recent Myocardial Infarction, Recent Stroke or Established Peripheral Arterial Disease, Acute Coronary Syndromes.
DOSAGE AND ADMINISTRATION
Acute Coronary Syndrome
Clopidogrel bisulfate tablets can be administered with or without food.
For patients with **non-ST-elevation ACS (UA/NSTEMI)**, initiate clopidogrel bisulfate tablets with a single 300 mg oral loading dose and then continue at 75 mg once daily. Initiate aspirin (75 to 325 mg once daily) and continue in combination with clopidogrel bisulfate.
For patients with **STEMI**, the recommended dose of clopidogrel bisulfate tablets is 75 mg once daily orally, administered in combination with aspirin (75 to 325 mg once daily), with or without thrombolytics. Clopidogrel bisulfate tablets may be initiated with or without a loading dose.
Recent MI, Recent Stroke, or Established Peripheral Arterial Disease
The recommended daily dose of clopidogrel bisulfate tablets are 75 mg once daily orally, with or without food.
CYP2C19 Poor Metabolizers
CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel.
Although a higher dose regimen in poor metabolizers increases antiplatelet response, an appropriate dose regimen for this patient population has not been established.
Use with Proton Pump Inhibitors (PPI)
Avoid using omeprazole or esomeprazole with clopidogrel bisulfate tablets. Omeprazole and esomeprazole significantly reduce the antiplatelet activity of clopidogrel bisulfate tablets. When concomitant administration of a PPI is required, consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite.
CONTRAINDICATION
Active Bleeding
Clopidogrel bisulfate tablets are contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.
Hypersensitivity
Clopidogrel bisulfate tablets are contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to clopidogrel or any component of the product.
WARNINGS AND PRECAUTIONS
Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function
Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 and by concomitant medications that interfere with CYP2C19.
Proton Pump Inhibitors
Avoid concomitant use of clopidogrel bisulfate with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of clopidogrel bisulfate.
General Risk of Bleeding
Thienopyridines, including clopidogrel bisulfate, increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue clopidogrel bisulfate five days prior to surgery. In patients who stopped therapy more than five days prior to CABG the rates of major bleeding were similar (event rate 4.4% clopidogrel bisulfate + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of CABG, the major bleeding rate was 9.6% for clopidogrel bisulfate + aspirin, and 6.3% for placebo + aspirin.
Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7 to 10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.
Discontinuation of Clopidogrel Bisulfate
Avoid lapses in therapy, and if clopidogrel bisulfate must be temporarily discontinued, restart as soon as possible. Premature discontinuation of clopidogrel bisulfate may increase the risk of cardiovascular events.
Patients with Recent Transient Ischemic Attack (TIA) or Stroke
In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and clopidogrel bisulfate has not been shown to be more effective than clopidogrel bisulfate alone, but the combination has been shown to increase major bleeding.
Thrombotic Thrombocytopenic Purpura (TTP)
TTP, sometimes fatal, has been reported following use of clopidogrel bisulfate, sometimes after a short exposure (<2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, macroangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever.

Cross - Reactivity among Thienopyridines
Hypersensitivity including rash, angioedema or hematologic reaction have been reported in patients receiving clopidogrel bisulfate, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines.

PREGNANCY AND LACTATION
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, respectively, on a mg/m 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 bisulfate should be used during pregnancy only if clearly needed.
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 from clopidogrel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS
CYP2C19 Inhibitors
Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain 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.
Proton Pump Inhibitors (PPI)
Avoid concomitant use of clopidogrel bisulfate with omeprazole or esomeprazole. In clinical studies, omeprazole was shown to reduce the antiplatelet activity of clopidogrel bisulfate when given concomitantly or 12 hours apart. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with clopidogrel bisulfate. Consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite.
Dexlansoprazole, lansoprazole and pantoprazole had less effect on the antiplatelet activity of clopidogrel bisulfate than did omeprazole or esomeprazole.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
Coadministration of clopidogrel bisulfate and NSAIDs increases the risk of gastrointestinal bleeding.
Warfarin (CYP2C9 Substrates)
Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, co-administration of clopidogrel bisulfate with warfarin increases the risk of bleeding because of independent effects on hemostasis.
However, at high concentrations in vitro, clopidogrel inhibits CYP2C9.
SSRIs and SNRIs
Since selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.

ADVERSE REACTIONS
The following are the common serious adverse reactions of Clopidogrel:
- Bleeding
-Thrombotic thrombocytopenic purpura

The following adverse reactions have been identified during post-approval use of clopidogrel bisulfate. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP), acquired hemophilia A
Eye disorders: Eye (conjunctival, ocular, retinal) bleeding
Gastrointestinal disorders: Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastric/duodenal ulcer, diarrhea
General disorders and administration site condition: Fever, hemorrhage of operative wound
Hepato-biliary disorders: Acute liver failure, hepatitis (non-infectious), abnormal liver function test
Immune system disorders: Hypersensitivity reactions, anaphylactoid reactions, serum sickness
Musculoskeletal, connective tissue and bone disorders: Musculoskeletal bleeding, myalgia, arthralgia, arthritis
Nervous system disorders: Taste disorders, fatal intracranial bleeding, headache
Psychiatric disorders: Confusion, hallucinations
Respiratory, thoracic and mediastinal disorders: Bronchospasm, interstitial pneumonitis, respiratory tract bleeding, eosinophilic pneumonia
Renal and urinary disorders: Increased creatinine levels
Skin and subcutaneous tissue disorders: Maculopapular, erythematous or exfoliative rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, skin bleeding, lichen planus, generalized pruritus
Vascular disorders: Vasculitis, hypotension
"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".
Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSAGE AND TREATMENT
Platelet inhibition by clopidogrel bisulfate is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in 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, prostration, difficult breathing, and gastrointestinal hemorrhage in animals.
Based on biological plausibility, platelet transfusion may restore clotting ability.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

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

AVAILABILITY
Clopidogrel Bisulfate (Deplatt) 75 mg Film-Coated Tablet-Alu-Alu Blister Pack of 10's (Box of 100's) - DRP-2681

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December 21, 2009

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torrent PHARMA

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