Lowplat® (Clopidogrel)

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COMPOSITION
LOWPLAT 75 mg Tablet
Each film coated tablet contains:
Clopidogrel……75 mg as Clopidogrel bisulfate USP.
LOWPLAT 300 mg Tablet
Each film coated tablet contains:
Clopidogrel……300 mg as Clopidogrel bisulfate USP.

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE
The effectiveness of Clopidogrel results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

DESCRIPTION
Clopidogrel bisulfate is a thienopyridine class inhibitor of P2Y12 ADP platelet receptors used as a platelet aggregation inhibitor (anti-platelet agent). Chemically it is methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)−acetate sulfate (1:1). The molecular formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S•H_2SO_4$

CLINICAL PHARMACOLOGY

Mechanism of Action
Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets.
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 P2Y12 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.

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. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/ml after a single 75 mg oral dose) occur approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Effect of Food
Clopidogrel can be administered with or without food. In a study in healthy male subjects when Clopidogrel 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 AUC0-24 was unchanged in the presence of food, while there was a 57% decrease in active metabolite Cmax. Similar results were observed when a Clopidogrel 300 mg loading dose was administered with a high fat breakfast.

Distribution
Clopidogrel and the main circulating (inactive) metabolite bind reversibly in vitro to human plasma proteins (98% and 94% respectively).

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. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.
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. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: 4-fold the dose results in 2.0 and 2.7-fold the Cmax and AUC, respectively.

Excretion
Following an oral dose of 14C- 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. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

INDICATIONS
• Acute coronary syndrome (ACS)
LOWPLAT (Clopidogrel) is indicated to reduce the rate of myocardial infarction (MI) and stroke in patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], (including patients who are to be managed medically and those who are to be managed with coronary revascularization). It should be administered in conjunction with aspirin.

LOWPLAT (Clopidogrel) is indicated to reduce the rate of myocardial infarction and stroke in patients with acute ST-elevation myocardial infarction (STEMI) (who are to be managed medically). It should be administered in conjunction with aspirin.

• Recent MI, recent stroke, or established peripheral artery disease
In patients with established peripheral arterial disease or with a history of recent myocardial infarction (MI) or recent stroke, LOWPLAT (Clopidogrel) is indicated to reduce the rate of MI and stroke.

• Prevention of atherothrombotic and thromboembolic events in atrial fibrillation
In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with oral Vitamin K antagonists (VKA) and who have a low bleeding risk, LOWPLAT (Clopidogrel) is indicated in combination with aspirin for the prevention of atherothrombotic and thromboembolic events, including stroke.

DOSAGE AND ADMINISTRATION

Acute Coronary Syndrome

− Non-ST segment elevation acute coronary syndrome (unstable angina [UA] or non-ST elevation myocardial infarction [NSTEMI]):
Clopidogrel treatment should be initiated with a single 300-mg loading dose and then continued at 75 mg once a day (with aspirin 75 mg-325 mg daily). Since higher doses of concomitant aspirin were associated with higher bleeding risk it is recommended that the dose of aspirin should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months

- ST segment elevation acute myocardial infarction:
Clopidogrel should be given as a single daily dose of 75 mg initiated with a 300-mg loading dose in combination with aspirin and with or without thrombolytics. For patients over 75 years of age, clopidogrel should be initiated without a loading dose.
Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with aspirin beyond four weeks has not been studied in this setting

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease
75 mg once daily orally without a loading dose

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation
In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg. Aspirin (75-100 mg daily) should be initiated and continued in combination with clopidogrel.

If a dose is missed:
− Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
− For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.

Dosage considerations in special populations

Renal impairment
Therapeutic experience is limited in patients with renal impairment to recommend any dosage adjustments. (See USE IN SPECIAL POPULATIONS)

Hepatic impairment
No dosing recommendations can be made in patients with hepatic impairment. Therapeutic experience is limited in patients with hepatic disease who have bleeding tendencies. (See USE IN SPECIAL POPULATIONS and CONTRAINDICATIONS)

Administration Requirements
For oral use. It may be given with or without food.

CONTRAINDICATIONS

Active bleeding
Clopidogrel is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

Hypersensitivity
Clopidogrel is contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to clopidogrel.

Severe hepatic impairment with bleeding tendencies
Clopidogrel is contraindicated in patients with severe hepatic impairment with bleeding tendencies

WARNINGS AND PRECAUTIONS

Diminished Antiplatelet Activity in Patients with Impaired CYP2C19 Function
Clopidogrel is a pro-drug. Inhibition of platelet aggregation by clopidogrel is achieved through an active (thiol) metabolite. CYP2C19 is involved in the formation of both the active thiol metabolite and the 2-oxo-clopidogrel intermediate metabolite. The metabolism of clopidogrel to its active thiol metabolite and resultant antiplatelet effects can be impaired by genetic variations in CYP2C19.
The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in Caucasian and Asian populations. Other alleles associated with absent or reduced metabolism are less frequent and include CYP2C19*4, *5, *6, *7, and *8. Patients homozygous for nonfunctional alleles of the CYP2C19 gene are termed "CYP2C19 poor metabolizers" and possess two loss-of-function alleles as defined above. Published frequencies for the poor CYP2C19 metabolizer genotypes are approximately 2% for Caucasians, 4% for Blacks and 14% for Chinese.
In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a diminished effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.
The metabolism of Clopidogrel can also be impaired by drugs that are moderate or strong inhibitors of CYP2C19, such as omeprazole or esomeprazole. Avoid concomitant use of Clopidogrel with these drugs because they significantly reduce the antiplatelet activity of Clopidogrel. (See DRUG INTERACTIONS)

General risk of bleeding
Thienopyridines, including clopidogrel, increase the risk of bleeding. Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days). Blood cell counts and/or other appropriate tests should be considered whenever clinical symptoms suggestive of bleeding arise during treatment. As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with aspirin, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs). The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the risk and intensity of bleedings.
Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians that they are taking clopidogrel before any surgery is scheduled.
Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).
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
Discontinuation of clopidogrel increases the risk of cardiovascular events. If clopidogrel must be temporarily discontinued (e.g., to treat bleeding or for surgery with a major risk of bleeding), restart it as soon as possible. When possible, interrupt therapy with clopidogrel for five to seven days prior to such surgery. Resume clopidogrel as soon as hemostasis is achieved.

Thrombotic thrombocytopenic purpura (TTP)
TTP, sometimes fatal, has been reported following use of Clopidogrel very rarely after a short exposure (<2 weeks). TTP is a serious condition that 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.

Cross-Reactivity among Thienopyridines
Hypersensitivity including rash, angioedema or hematologic reactions such as thrombocytopenia and neutropenia has been reported in patients receiving Clopidogrel, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines such as ticlopidine, prasugrel etc. Monitoring for signs/symptoms of hypersensitivity is advised.

Acquired hemophilia
Acquired hemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired hemophilia should be considered. Patients with a confirmed diagnosis of acquired hemophilia should be managed and treated by specialists, and clopidogrel should be discontinued

Effects on ability to drive and use machines
Clopidogrel has no or negligible influence on the ability to drive and use machines.

ADVERSE REACTIONS

Blood and lymphatic system disorders
Uncommon: Thrombocytopenia, leucopenia, eosinophilia
Rare: Neutropenia, including severe neutropenia
Very rare: Thrombotic thrombocytopenic purpura (TTP), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia.
Immune system disorders
Very rare: Serum sickness, anaphylactoid reactions,
Not known: cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel)
Psychiatric disorders
Very rare: Hallucinations, confusion
Nervous system disorders
Uncommon: Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness.
Very rare: taste disturbances
Eye disorders
Uncommon: Eye bleeding (conjunctival, ocular, retinal)
Ear and labyrinth disorders
Rare: Vertigo
Vascular disorders
Common: Hematoma
Very rare: Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders
Common: Epistaxis
Very rare: Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
Gastrointestinal disorders
Common: Gastrointestinal hemorrhage, diarrhea, abdominal pain, dyspepsia
Uncommon: Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence
Rare: Retroperitoneal hemorrhage
Very rare: Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepatobiliary disorders
Very rare: Acute liver failure, hepatitis, abnormal liver function test
Skin and subcutaneous tissue disorders
Common: Bruising
Uncommon: Rash, pruritus, skin bleeding (purpura)
Very rare: Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)), angioedema, induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus.
Reproductive system and breast disorders
Rare: Gynaecomastia
Musculoskeletal, connective tissue and bone disorders
Very rare: Musculo-skeletal bleeding (hemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders
Uncommon: Haematuria
Not known: Glomerulonephritis, blood creatinine increased
General disorders and administration site conditions
Common: Bleeding at puncture site
Very rare: Fever
Investigations
Uncommon: Bleeding time prolonged, neutrophil count decreased, platelet count decreased.

DRUG INTERACTIONS

CYP2C19 Inhibitors
Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that are moderate or potent inhibitors of this enzyme result in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition and therapeutic effect

Omeprazole or esomeprazole
Avoid concomitant use of clopidogrel with omeprazole or esomeprazole. Omeprazole has shown to reduce significantly the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. Dexlansoprazole, lansoprazole and pantoprazole has less effect on the antiplatelet activity of clopidogel than omeprazole or esomeprazole.

Other drugs
Other drugs that are moderate/strong inhibitors of CYP2C19 include fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz. Concomitant use of these drugs is not recommended with Clopidogrel.

Non-steroidal anti-inflammatory drugs (NSAIDs)
Coadministration of clopidogrel and NSAIDs including COX-2 inhibitors increases the risk of gastrointestinal bleeding.

Warfarin (CYP2C9 Substrates)
Although 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, coadministration of clopidogrel 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
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.

Repaglanide (CYP2C8 Substrates)
The acyl-β-glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C8. Clopidogrel can increase the systemic exposure to drugs that are primarily cleared by CYP2C8, thereby needing dose-adjustment and/or appropriate monitoring. Concomitant administration of clopidogrel with repaglinide significantly increases systemic exposures to repaglinide. When concomitant use is required in a patient maintained on clopidogrel, initiate repaglinide at 0.5 mg with each meal and titrate based on blood glucose levels. Do not exceed a total daily dose of 4 mg. If concomitant use of clopidogrel is required in a patient stabilized on higher doses of repaglinide, down titrate the dose of repaglinide based on blood glucose levels to not exceed a total daily dose of 4 mg

Aspirin
A pharmacodynamic interaction between clopidogrel and aspirin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, clopidogrel and aspirin have been administered together for up to one year. (See DOSAGE AND ADMINISTRATION)

Heparin
A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Monitoring and caution is advised
Patients receiving Glycoprotein IIb/IIIa inhibitors
Clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors.

Patients receiving Glycoprotein IIb/IIIa inhibitors
Clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors.

Thrombolytics
The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins has been assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding is similar to that when thrombolytic agents and heparin are co-administered with aspirin

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA Pregnancy Category B. No adequate and well-controlled studies are available in pregnant women. Clopidogrel should be used during pregnancy only if clearly needed.

Nursing mothers
It is not known whether clopidogrel 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.

Pediatric use
Safety and effectiveness in pediatric populations have not been established.

Geriatric use
No dosage adjustment is necessary in elderly patients.

Renal impairment
Experience is limited in patients with renal impairment. Some data reveals that after repeated doses of 75 mg clopidogrel per day in patients with severe renal disease (creatinine clearance from 5 to 15 ml/min) and moderate renal impairment (creatinine clearance from 30 to 60 mL/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients. No dosing recommendations can be made.

Hepatic impairment
No dosage adjustments can be made in patients with hepatic impairment. After repeated doses of 75 mg clopidogrel 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. Therapeutic experience is limited in patients with hepatic disease who have bleeding tendencies. Clopidogrel is contraindicated in patients with severe hepatic impairment having bleeding tendencies.

OVERDOSAGE

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Platelet inhibition by clopidogrel is irreversible and will last for the life of the platelet. Appropriate therapy should be considered if bleedings are observed. No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

PRESENTATION

LOWPLAT 75mg is Available in pack of 10 film-coated tablets.
LOWPLAT 300mg is Available in pack of 2 film-coated tablets.

INSTRUCTIONS

Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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ڈاکٹری ہدایات کے مطابق استعمال کریں۔
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