Lowplat Plus®

(Clopidogrel & Aspirin)

لوپلیٹ پلس

COMPOSITION
LOWPLAT PLUS 75 Tablet
Each film coated tablet contains:
Clopidogrel……75 mg as Clopidogrel bisulfate USP
Aspirin……..75 mg as enteric coated
(PharmEvo Specs.)

LOWPLAT PLUS 150 Tablet
Each film coated tablet contains:
Clopidogrel……75 mg as Clopidogrel bisulfate USP
Aspirin……..150 mg as enteric coated
(PharmEvo Specs.)

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
Lowplat Plus is a fixed-dose bi-layered combination containing Clopidogrel and Enteric Coated Aspirin.

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 $C_{16}H_{16}ClNO_2S•H_2SO_4$.

Aspirin [acetylsalicylic acid (ASA)] is a nonsteroidal anti-inflammatory drug indicated to reduce the risk of death and myocardial infarction (MI) in patients with chronic coronary artery disease, such as patients with a history of MI or unstable angina pectoris or with chronic stable angina and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or transient ischemic attack.

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 is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. 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.

Aspirin inhibits prostaglandin synthesis resulting in inhibition of platelet aggregation for their lifespan of about 7-10 days. The acetyl group of aspirin binds with a serine residue of cyclooxygenase-1 (COX-1), resulting in irreversible inactivation of the enzyme. Inhibition of COX-1 prevents conversion of arachidonic acid to thromboxane A2 (TXA2), which is a potent agonist of platelet aggregation.

Pharmacokinetics

Clopidogrel
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.

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.

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

Aspirin
Absorption
Following absorption, the aspirin in Lowplat plus is hydrolysed to salicylic acid with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels are essentially undetectable 1.5-3 hours after dosing.

Distribution
Aspirin is poorly bound to plasma proteins and its apparent volume of distribution is low (10 l). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At low concentrations (<100 micrograms/ml), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and foetal tissues.

Biotransformation and Elimination
The aspirin in Lowplat Plus is rapidly hydrolysed in plasma to salicylic acid, with a half-life of 0.3 to 0.4 hours for Aspirin doses from 75 to 100 mg. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid in Lowplat Plus has a plasma half-life of approximately 2 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide.

INDICATIONS
Lowplat Plus is indicated for the prevention of ischemic events, myocardial infarction, stroke and cardiovascular death in patients with Acute Coronary Syndrome (ACS).

Clopidogrel/Aspirin is indicated for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA).

Lowplat Plus is a fixed-dose combination medicinal product for continuation of therapy in:
• Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) including patients undergoing a stent placement following percutaneous Coronary intervention.
• ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy.

DOSAGE AND ADMINISTRATION

Clopidogrel/Aspirin fixed-dose combination is used following initiation of therapy with clopidogrel and ASA given separately and replaces the individual clopidogrel and ASA products.
• In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Qwave myocardial infarction): 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. If the use of Clopidogrel/Aspirin is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.
• In patients with ST segment elevation acute myocardial infarction: 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 ASA beyond four weeks has not been studied in this setting. If the use of Clopidogrel/Aspirin is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

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

Paediatric Population
The safety and efficacy of Clopidogrel/Aspirin in children and adolescents under 18 years old have not been established. Clopidogrel/Aspirin is not recommended in this population.

Renal impairment
Clopidogrel/Aspirin must not be used in patients with severe renal impairment. Therapeutic experience is limited in patients with mild to moderate renal impairment. Therefore Clopidogrel/Aspirin should be used with caution in these patients.

Hepatic impairment
Clopidogrel/Aspirin must not be used in patients with severe hepatic impairment. Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Therefore Clopidogrel/Aspirin should be used with caution in these patients.

CONTRAINDICATIONS
Due to the presence of both components of the medicinal product, Clopidogrel/Aspirin is contraindicated in case of:

• Hypersensitivity to the active substances or to any of the excipients.
• Severe hepatic impairment.
• Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

In addition, due to the presence of ASA, its use is also contraindicated in:
• Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and syndrome of asthma, rhinitis, and nasal polyps. Patients with pre-existing mastocytosis, in whom the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting).
• Severe renal impairment (creatinine clearance <30 ml/min).
• Third trimester of pregnancy.

WARNINGS AND PRECAUTIONS

Bleeding and haematological disorders
Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment. As a dual antiplatelet agent, Clopidogrel/Aspirin 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 other NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), CYP2C19 strong inducers, thrombolytics, or other medicinal products associated with bleeding risk such as pentoxifylline.

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. The concomitant administration of Clopidogrel/Aspirin with oral anticoagulants is not recommended since it may increase the intensity of bleeding.

Patients should inform physicians and dentists that they are taking Clopidogrel/Aspirin before any surgery is scheduled and before any new medicinal product is taken. Where elective surgery is being considered, the need for dual antiplatelet therapy should be reviewed and consideration given to the use of a single antiplatelet agent. If patients must temporarily stop antiplatelet therapy, Clopidogrel/Aspirin should be discontinued 7 days prior to surgery.

Clopidogrel/Aspirin prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Patients should also be told that it might take longer than usual to stop bleeding when they take Clopidogrel/Aspirin, and that they should report any unusual bleeding (site or duration) to their physician.

Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

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

Recent transient ischaemic attack or stroke
In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of ASA and clopidogrel has been shown to increase major bleeding. Therefore, such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

Cytochrome P450 2C19 (CYP2C19)
Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged.

Use of medicinal products that induce the activity of CYP2C19 would be expected to result in increased drug levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged.

CYP2C8 substrates
Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products.

Cross-reactions among thienopyridines
Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported. Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

Caution required due to ASA
• In patients with a history of asthma or allergic disorders since they are at increased risk of hypersensitivity reactions.
• In patients with gout since low doses of ASA increase urate concentrations.
• In children under 18 years of age, there is a possible association between ASA and Reye's syndrome. Reye's syndrome is a very rare disease which can be fatal.
• This medicinal product must be administered under close medical supervision in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to risk of haemolysis.
• Alcohol may increase the risk of gastrointestinal injury when taken with ASA. Patients should be counselled about the risks of gastrointestinal injury and bleeding while taking clopidogrel plus aspirin with alcohol, especially if alcohol consumption is chronic or heavy.

Gastrointestinal (GI)
Clopidogrel/Aspirin should be used with caution in patients with a history of peptic ulcer or gastroduodenal haemorrhage or minor upper GI symptoms as this may be due to gastric ulceration which may lead to gastric bleeding. GI undesirable effects including stomach pain, heartburn, nausea, vomiting, and GI bleeding may occur. Minor GI symptoms, such as dyspepsia, are common and can occur anytime during therapy. Physicians should remain alert

for signs of GI ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be told about the signs and symptoms of GI undesirable effects and what steps to take if they occur.

In patients concomitantly receiving nicorandil and NSAIDs including ASA and LAS, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage.

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
Very rare: Hearing loss or tinnitus
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, liver injury, 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: Renal failure, acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics), 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
Medicinal products associated with bleeding risk
There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution.

Oral anticoagulants
The concomitant administration of Clopidogrel/Aspirin with oral anticoagulants is not recommended since it may increase the intensity of bleeding. Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on haemostasis.

Heparin
In a clinical study conducted in healthy subjects, 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 the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between Clopidogrel/Aspirin and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Thrombolytics
The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with aspirin. The safety of the concomitant administration of clopidogrel/aspirin with other thrombolytic agents has not been formally established and should be undertaken with caution.

NSAIDs
In a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. Consequently, the concomitant use of NSAIDs including Cox-2 inhibitors is not recommended.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

SSRIs
Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

Other concomitant therapy with clopidogrel

Inducers of CYP2C19
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that induce the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel.

Rifampicin strongly induces CYP2C19 resulting to both an increase level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged.

Inhibitors of CYP2C19
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged.

Medicinal products that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.

Proton Pump Inhibitors (PPI)
Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel.

Anti-retroviral therapies (ART)
A significantly lower exposure to clopidogrel active metabolite and reduced platelet inhibition have been demonstrated in HIV-infected patients treated with ritonavir- or cobicistat-boosted anti-retroviral therapies. Although the clinical relevance of these findings is uncertain, there have been spontaneous reports of HIV-infected patients treated with boosted ART, who have experienced re-occlusive events after de-obstruction or have suffered thrombotic events under a clopidogrel loading treatment schedule. Exposure of clopidogrel and average platelet inhibition can be decreased with concomitant use of ritonavir. Therefore, concomitant use of clopidogrel with boosted ART should be discouraged.

Other concomitant therapy with Aspirin
Interactions with the following medicinal products have been reported with Aspirin:

Uricosurics (benzbromarone, probenecid, sulfinpyrazone)
Caution is required because Aspirin may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

Methotrexate
Due to the presence of Aspirin, methotrexate used at doses higher than 20 mg/week should be used with caution as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

Tenofovir
Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.

Valproic acid
The concomitant administration of salicylates and valproic acid may result in decreased valproic acid protein binding and inhibition of valproic acid metabolism resulting in increased serum levels of total and free valproic acid.

Other interactions with ASA
Interactions with the following medicinal products with higher (anti-inflammatory) doses of ASA have also been reported: angiotensin converting enzyme (ACE) inhibitors, phenytoin, beta blockers, diuretics, and oral hypoglycemic agents.

Alcohol
Alcohol may increase the risk of gastrointestinal injury when taken with aspirin. Patients should be counselled about the risks of gastrointestinal injury and bleeding while taking clopidogrel plus ASA with alcohol, especially if alcohol consumption is chronic or heavy.

USE IN SPECIAL POPULATIONS

Pregnancy
No clinical data on exposure to clopidogrel/acetylsalicylic acid during pregnancy are available. Clopidogrel/Aspirin should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with clopidogrel/ASA.

Due to the presence of Aspirin, Lowplat Plus is contraindicated during the third trimester of pregnancy.

Clopidogrel:
As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Aspirin:
Low doses (up to 100 mg/day):
Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Nursing mothers
It is not known whether clopidogrel is excreted in human milk. Animal studies have shown excretion of clopidogrel in breast milk. ASA is known to be excreted in limited amounts in human milk. Breast-feeding should be discontinued during treatment with Clopidogrel/Aspirin.

Overdose

Clopidogrel
Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. 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.

Aspirin
The following symptoms are associated with moderate intoxication: dizziness, headache, tinnitus, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain).

The following symptoms can also arise: hyperthermia and perspiration, leading to dehydration, restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system can lead to coma, cardiovascular collapse and respiratory arrest. The lethal dose of acetylsalicylic acid is 25-30 g. Plasma salicylate concentrations above 300 mg/l (1.67 mmol/l) suggest intoxication.

Overdose with aspirin/clopidogrel fixed dose combination may be associated with increased bleeding and subsequent bleeding complications due to the pharmacological activity of clopidogrel and aspirin.

Non-cardiogenic pulmonary edema can occur with acute and chronic acetylsalicylic acid overdose.

If a toxic dose has been ingested then admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting; if this fails, gastric lavage is indicated. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalising of the urine (250 mmol sodium bicarbonate for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

PRESENTATION
Lowplat Plus 75mg : Pack of 10 film coated tablets.
Lowplat Plus 150mg : Pack of 10 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

ہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔
دوا کے ممکنہ منفی اثرات کے متعلق reports@pharmevo.biz
پر مطلع کریں۔

ہماری ادویات کی مزید معلومات کے لئے فارم اسسٹ کی
ہیلپ لائن نمبر 0800-82222 پر کال کریں۔
پیر تا جمعہ صبح 9:00 بجے تا شام 6:00 بجے
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