Pidogrel™
(Clopidogrel)

Highnoon

COMPOSITION
Pidogrel 75mg Tablet:
Each film-coated tablet contains:
Clopidogrel Bisulphate 97.87mg equivalent to Clopidogrel 75mg

DESCRIPTION
Pidogrel (clopidogrel bisulfate) is a thienopyridine class inhibitor of P2Y12 ADP platelet receptors.

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.

PHARMACOKINETICS
Clopidogrel is rapidly but incompletely absorbed after oral doses, absorption appears to be at least 90%. It is prodrug and extensively metabolized in the liver, mainly to the inactive carboxylic acid derivatives. Metabolism is mediated by cytochrome P450 isoenzymes including CYP3A4 and CYP2B6, CYP1A2, CYP1A1 and CYP2C19. The active metabolite appears to be a thiol derivatives, it has been identified in vitro but appears to be too unstable to the isolated from plasma. Clopidogrel and 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 AND USAGE
It is indicated in the following condition;

- Acute Coronary Syndrome (ACS)
  - 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.
  - 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 Arterial Disease
  - To reduce the rate of MI and stroke in patients with established peripheral arterial disease or with a history of recent myocardial infarction (MI) or recent stroke.
- Prevention of atherothrombotic and thromboembolic events in patients with atrial fibrillation and at least one risk factor for a vascular event (with aspirin) and for whom warfarin is unsuitable
- Prevention of atherothrombotic events in percutaneous coronary intervention (adjunct with aspirin) in patients not already on clopidogrel
- Prevention of atherothrombotic events in peripheral arterial disease or within 35 days of myocardial infarction, or within 6 months of ischemic stroke

DOSAGE AND ADMINISTRATION
- Acute Coronary Syndrome
  - In patients who need an antiplatelet effect within hours, initiate pidogrel (clopidogrel) with a single 300 mg oral loading dose and then continue at 75 mg once daily. Initiating pidogrel (clopidogrel) without a loading dose will delay establishment of an antiplatelet effect by several days.
- 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 patients with atrial fibrillation and at least one risk factor for a vascular event (with aspirin) and for whom warfarin is unsuitable
  - 75 mg once daily
- Prevention of atherothrombotic events in percutaneous coronary intervention (adjunct with aspirin) in patients not already on clopidogrel
  - Loading dose 300 mg, to be taken prior to the procedure, alternatively loading dose 600 mg, higher dose may produce a greater and more rapid inhibition of platelet aggregation
- Prevention of atherothrombotic events in peripheral arterial disease or within 35 days of myocardial infarction, or within 6 months of ischemic stroke
  - 75 mg once daily

CONTRAINDICATIONS
- It is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial haemorrhage.
- It is contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to clopidogrel or any component of the product.

WARNINGS AND PRECAUTIONS
- *Diminished Antiplatelet Activity in Patients with 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. The metabolism of clopidogrel can also be impaired by drugs that inhibit CYP2C19, such as omeprazole or esomeprazole. Avoid concomitant use of clopidogrel with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of clopidogrel.
- *General Risk of Bleeding:* P2Y12 inhibitors (Thienopyridines) including clopidogrel, increase the risk of bleeding. Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days). 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. Use of drugs 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, avoid concomitant use of strong CYP2C19 inducers. Risk factors for bleeding include concomitant use of other drugs that increase the risk of bleeding (e.g. anticoagulants, anti-platelet agents, and chronic use of NSAIDs).
- *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 days prior to such surgery. Resume it as soon as hemostasis is achieved.
- *Thrombotic Thrombocytopenic Purpura (TTP):* TTP, sometimes fatal, has been reported following use of clopidogrel, 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, 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 reaction has been reported in patients receiving clopidogrel, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines.

ADVERSE REACTIONS
The reported adverse events are bleeding including fatal bleeding, thrombotic thrombocytopenic purpura, intracranial haemorrhage, haemorrhagic strokes, intraocular bleeding with significant loss of vision, cerebral or noncerebral bleeding, epistaxis, hematoma, skin reaction, diarrhoea, constipation, dizziness, leucopenia, vomiting, nausea, paraesthesia, neutropenia and pruritus. The additional reported events are agranulocytosis, aplastic anaemia/pancytopenia,, acquired hemophilia A, bone marrow disorder, gynaecomastia, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, taste altered, gastric/duodenal ulcer, fever, acute liver failure, hepatitis (noninfectious), abnormal liver function test, hypersensitivity reactions, anaphylactoid reactions, serum sickness, insulin autoimmune syndrome, which can lead to severe hypoglycemia, myalgia, arthralgia, arthritis, taste disorders, headache, ageusia, confusion, hallucinations, vertigo, bronchospasm, interstitial pneumonitis, eosinophilic pneumonia, increased creatinine levels, 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, lichen planus, generalized pruritus, vasculitis, Kounis syndrome, glomerulonephritis and hypotension.

DRUG INTERACTIONS
- Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of 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.
- Avoid concomitant use of Clopidogrel with omeprazole or esomeprazole. Dexlansoprazole, lansoprazole, and pantoprazole had less effect on the antiplatelet activity of Clopidogrel than did omeprazole or esomeprazole.
- As with other oral P2Y12 inhibitors, coadministration of opioid agonists delay and reduce the absorption of clopidogrel, presumably because of slowed gastric emptying, resulting in reduced exposure to its metabolites. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring coadministration of morphine or other opioid agonists.
- Coadministration of Clopidogrel and NSAIDs increases the risk of gastrointestinal bleeding.
- 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, coadministration of Clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.
- 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.
- 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 appropriate monitoring. Clopidogrel increased repaglinide exposures by 3.9-fold to 5.1-fold. Avoid concomitant use of repaglinide with Clopidogrel. If concomitant use cannot be avoided, initiate repaglinide at 0.5 mg before each meal and do not exceed a total daily dose of 4 mg. Increased frequency of glucose monitoring may be required during concomitant use.
- Since Clopidogrel is metabolized to its active metabolite partly by CYP2C19, use of drugs that include the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel. Rifampin 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, avoid concomitant use of strong CYP2C19 inducers.
- Co-administration of anti-platelet agents increase the risk of bleeding due to an additive effect. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with other anti-platelet agents.

USE IN SPECIFIC POPULATIONS
Pregnancy
Clopidogrel use during labour or delivery will increase the risk of maternal bleeding and haemorrhage. Avoid neuraxial blockade during clopidogrel use because of the risk of spinal hematoma. When possible, discontinue clopidogrel 5 to 7 days prior to labour, delivery, or neuraxial blockade. Myocardial infarction and stroke are medical emergencies. Therapy for the pregnant woman should not be withheld because of potential concerns regarding the effects of clopidogrel on the fetus.

Lactation
There are no data on the presence of clopidogrel in human milk or the effects on milk production. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with mother's clinical need for clopidogrel and any potential adverse effects on the breastfed infant from clopidogrel or from underlying maternal condition.

Paediatric Use
The safety and effectiveness of ticagrelor in paediatric patients have not been established.

Geriatric Use
No dosage adjustment is necessary in elderly patients.

Hepatic Impairment
No dosage adjustment is necessary in patients with hepatic impairment.

Renal Impairment
Experience is limited in patients with severe and moderate renal impairment.

OVERDOSAGE
Platelet inhibition by clopidogrel is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal haemorrhage in animals. Based on biological plausibility, platelet transfusion may restore clotting ability.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Pidogrel 75mg Tablets: Alu. Alu. Blister Pack of 1 x 10's.

پیڈوگرِل™

(کلوپیڈوگرِل)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
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