FRONT

178 MM

140 MM

FULL PRESCRIBING INFORMATION

Clopidogrel + Aspirin

Clotisprin

75 mg/75 mg Capsule
Antithrombotic Agent
(Platelet Aggregation Inhibitor)

FORMULATION
Each hard gelatin capsule contains:
Clopidogrel Bisulfate USP
Eq. to Clopidogrel.....75 mg
(as immediate-release pellets)
Aspirin BP.....75 mg
(as enteric-coated pellets)
Excipients.....q.s.

Colours: Sunset yellow & Titanium Dioxide.
Approved colours used in hard gelatin capsule shell.

PHARMACODYNAMIC PROPERTIES:
MECHANISM OF ACTION
Clopidogrel is an inhibitor of platelet aggregation.
A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established atheroschlerotic cardiovascular disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, or need for bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate. The salicylates alleviate pain by virtue of both a peripheral and a central nervous system effect. Salicylates, by inhibiting the synthesis of prostaglandins that occur in inflamed tissues, prevent the sensitization of pain receptors to mechanical stimulation or to chemical such as bradykinin, that appear to mediate the pain response. Direct effects on the central nervous system have been described and suggest a hypothalamic site for the analgesic as well as the antipyretic effects.

PHARMACOKINETIC PROPERTIES:
Aspirin:
Absorption after oral administration of a solution of aspirin is usually complete, while enteric-coated capsule are less reliably absorbed. Absorption of aspirin formulated as regular unbuffered capsules is intermediate between that of solution and of enteric-coated preparations and is usually greater than 80%. Presystemic metabolism of aspirin to salicylate results in little or no systemic availability of low oral doses, and is believed that aspirin in portal venous blood accounts for the effect of low doses on platelets. After 500 mg, peak plasma concentration of aspirin are achieved in about 14 minutes, while peak salicylic acid concentration are obtained at 0.5 to 1 h after dosing. The plasma half-life of aspirin is 15-20 min., salicylic acid exhibits dose-dependent kinetics, the apparent half-life after a 300 mg dose being around 3 h, after 1 g dose, around 5-6 h, after a 10 g dose around 20 h. The volume of distribution of aspirin is 0.15-0.21 kg^{-1}. Protein binding of aspirin occurs to an unknown but variable extent that is time as well as concentration dependent. Plasma albumin is acetylated by aspirin. Salicylates is also variably bound to plasma protein, the percentage bound decreasing with concentration. Salicylate penetrates into the breast milk, saliva, joint fluids, and cerebrospinal fluid, being detectable in concentration approximately 1.5 times those of blood in these fluids. Fetal levels exceed concentration in maternal plasma.

Oral Absorption > 80%
Presystemic metabolism high
Plasma half-life range 15-20 min
(salicylate: 3-20 h)
Volume of distribution 0.21 kg^{-1}
Plasma protein binding variable

Concentration-effect relationship:
Antipyretic and analgesic effects occur at plasma concentrations of salicylate of 200 ng. 1-1 and anti-inflammatory effects increase up to 350 ng. 1-1, the antiplatelet effect of aspirin is not directly related to plasma concentration, this effect is irreversible and cumulative. Studies with intravenous doses of salicylate suggest that it has little effect upon prosticycline or thromboxane synthesis *in-vivo.*
Metabolism: Aspirin is rapidly converted by esterases present in plasma and many tissues, especially liver; to salicylic acid which itself has some antipyretic, analgesic and inflammatory actions, but which has little effect on platelets. Salicylic acid is metabolized in the liver to the glycine conjugate salicyluric acid. Other metabolites include salicyl phenolic glucuronide, salicyl acyl glucuronide and gentisic acid. Excretion of salicylic acid in urine in pH dependent approximately 80% appears unchanged in the urine at pH 8, but only 10% at pH 4.

Clopidogrel:
After repeated 75 mg oral dose of clopidogrel (base), plasma concentration of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.00025mg/L) beyond 2 hours after dosing. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative and it too has no effect on platelet aggregation. It represents about 85% of the circulating drug related compounds in plasma.
Following an oral dose of 14 C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days.

Effect of food: Administration of clopidogrel bisulfate with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolites.
Absorption and Distribution: Clopidogrel is rapidly absorbed after oral administration of repeated dose of 75 mg clopidogrel (base), with peak plasma levels (3 mg/L) of the main circulating metabolite occurring approximately 1 hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentration increased in proportion to dose) in dose range of 50 to 150 mg of clopidogrel Absorption is at least 50% based on urinary excretion of clopidogrel related metabolites. Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma protein (98% and 94% respectively). The binding is non saturable *in-vitro* up to a concentration of 100 pglmL.
Metabolism and Elimination: *In vitro* and *in-vivo*, clopidogrel undergoes rapid hydrolysis into carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

Special Population:
Geriatric Patients: Plasma concentration of the main circulating metabolite are significantly higher in elderly compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.
Renally Impaired Patients: After repeated dose of 75 mg clopidogrel bisulfate per day, plasma levels of the main circulating metabolite were lower in patient with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of clopidogrel per day. No dosage adjustment is needed in renally impaired patients.
Gender: No significant difference was observed in the plasma levels of the main circulating metabolite between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, clinical study (clopidogrel vs aspirin in patients at risk of ischemic events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, abnormal clinical laboratory parameters was similar in men and women.
Race: Pharmacokinetic differences due to race have not been studied.

INDICATIONS:
For the reduction of thrombotic events in patients with recent myocardial infarction, recent stroke, or established peripheral arterial disease and indicated for acute coronary syndrome.

CONTRAINDICATIONS:
Clopidogrel + Aspirin is contraindicated in patients with:
a. Hypersensitivity to clopidogrel
b. Hypersensitivity to aspirin and/or non-steroidal anti-inflammatory agents.
c. Recent history of gastrointestinal bleeding
d. Active pathological bleeding such as peptic ulcer or intracranial hemorrhage, or bleeding disorders like hemophilia.

DOSAGE AND ADMINISTRATION:
Prevention of ischemic events:
The recommended dose is one capsule once daily.
Acute coronary syndrome:
Maintenance: One capsule daily.
Or as prescribed by the physician.

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WARNINGS AND SPECIAL PRECAUTIONS:
CLOPIDOGREL
Thrombotic thrombocytopenic purpura (TTP): TTP has been reported rarely following use of Clopidogrel bisulfate, sometimes after a short exposure (< 2 weeks). TTP is a serious condition requiring prompt treatment. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes fragmented RBCs) seen on peripheral smear, neurological findings, renal dysfunction, and fever. TTP was not seen during clopidogrel's clinical trials, which included over 11,300 clopidogrel-treated patients. In world-wide post marketing experience, however, TTP has been reported at a rate of about four cases per million patients exposed, or about 11 cases per million exposed, or about 11 cases per million patient-years. The background rate is thought to be about four cases per million person-years.

ASPIRIN:
This medicinal product may be used in the following circumstances only after strict consideration of the risk benefit ratio:
• First and second trimester of the pregnancy; During breastfeeding when using high doses of aspirin (> 300 mg/day).
• Hypersensitivity to anti-inflammatory or antirheumatic drugs and other allergens.
• In the presence of concomitant treatment with aspirin except low-dose heparin therapy.
• In the presence of severe liver or kidney damage.
• In patients with a history of gastrointestinal disorders.

GI bleeding:
The combination of Clopidogrel & Aspirin prolongs the bleeding time. So, it should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions (such as aspirin and other NSAIDs) should be used with caution in patients taking clopidogrel.
Reye's syndrome: Reye's syndrome may develop in individuals who have chicken pox, influenza or flu symptoms. This combination is not recommended for use in patients with chicken pox, influenza or flu symptoms.
Nasal polyps or nasal allergies:
The combination of Clopidogrel & Aspirin should be administered with caution to patients with nasal polyps or nasal allergies. In patients receiving large doses of aspirin and/ or prolonged therapy, mild salicylate intoxication (salicylism) may develop and may be reversed by reduction in dosage.
General:
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. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, clopidogrel should be discontinued 7 days prior to surgery.
Hepatic and Renal Impairment:
The combination of Clopidogrel & Aspirin should be avoided in patients with impaired hepatic and renal function. Aspirin causes sodium and water retention in patients with renal impairment and increases the risk of gastrointestinal bleeding.

ADVERSE DRUG REACTIONS:
The drug is generally well-tolerated. Side effects that have been reported include abdominal pain, dyspepsia, gastritis, diarrhea, nausea, vomiting, constipation, gastrointestinal hemorrhage, ulceration, neurotropenia, rash, palpitation, syncope, drowsiness, asthenia, neuralgia, paresthesia and vertigo.
Pregnancy:
Adverse effects are increased in the mother and the fetus following chronic ingestion of aspirin.
Because of possible adverse effects on the neonate and the potential for increased maternal blood loss, the combination of Clopidogrel & Aspirin should be avoided during the last three months of pregnancy.
Lactation:
The combination of Clopidogrel & Asipirin should be avoided in nursing mothers because of the possible risk of developing Reye's syndrome. Regular use of high dose of aspirin cold impair platelet function and produce hypoprothrombinemia in infants if neonatal vitamin K levels are low.
Pediatric Use:
Safety and effectiveness of this combination in the pediatric population have not been established.

DRUG INTERACTIONS:
Oral anticoagulants: The combination of Clopidogrel & Aspirin should be used with caution when anticoagulants are prescribed concurrently, since both aspirin and clopidogrel may depress the concentration of prothrombin in plasma and thereby increase bleeding time.
Hypoglycemic agents: Large doses of salicylates have hypoglycemic action and may enhance the effect of the oral hypoglycemic. Consequently, they should not be given concomitantly; if however this is necessary, the dosage of hypoglycemic agent must be reduced while the salicylates are given.
Non-Steroidal Anti-inflammatory drugs (NSAIDs):
In healthy volunteers receiving naproxen, concomitant administration of clopidogrel was associated with increased occult gastrointestinal blood loss. NSAIDs and clopidogrel should be co-administered with caution. The combination of Clopidogrel & Aspirin is contraindicated in patients who are hypersensitive to NSAIDs.
Uricosuric agents: Although Salicylates in larger doses are uricosuric agents, smaller amounts may decrease the uricosuric effects of probenecid, sulfinpyrazone and phenylbutazone. Aspirin may decrease the effects of probenecid, sulfinpyrazone and phenylbutazone.

Spironolactone: Sodium excretion produced by spironolactone may be decreased in the presence of salicylates. Salicylates can produce changes in thyroid function test. Salicylates should be used with caution in patients with severe hepatic damage, pre-existing hypoprothrombinemia or Vitamin K deficiency and in those undergoing surgery.
Alcohol: Has a synergistic effect with aspirin with corticosteroids by increasing the risk of gastrointestinal bleeding.
Corticosteroids: Concomitant administration of aspirin with corticosteroids may increase the risk of gastrointestinal ulceration and may reduce serum salicylate level.
Pyrazolone derivatives (Phenylbutazone, Oxyphenylbutazone and possibly Dipyrone):
Concomitant administration may increase the risk of gastrointestinal ulceration.
Urinary alkalinizers: Decrease aspirin effectiveness by increasing the risk of salicylate renal excretion.
Phenobarbital: Decrease aspirin effectiveness by enzyme induction.
Phenytoin, Tamoxifen, Tolbutamide, Torsenamide,
Fluvastatin: At high concentration *in-vitro*, clopidogrel inhibits P450 (2C9). Accordingly, clopidogrel may interfere with metabolism of Phenytoin, Tamoxifen, Tolbutamide, Torsenamide and Fluvastatin, but there are no data with which to predict the magnitude of these interactions.
Caution should be used when any of these drugs is co-administered with clopidogrel. Aspirin may also increase serum levels of phenytoin.

OVERDOSE AND TREATMENT:
Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleeding is 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 overdose symptoms include dizziness, tinnitus, sweating, nausea, vomiting, altered glucose metabolism, mental confusion, hyperventilation, respiratory alkalosis, metabolic acidosis, ketosis, fluid, and electrolyte losses.
Depression of the central nervous system may lead to coma, cardiovascular collapse and respiratory failure. Gastric lavage, forced alkaline diuresis, restoration of fluid, electrolyte and acid balance, dialysis and supportive therapy may be required.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.
KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

AVAILABILITY:
Alu/Alu Blister Pack x 10's (Box of 100's)

DRP-10573
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