120mm

181mm

Clopisel 75mg Tablet

(C l o p i d o g r e l)

کلوپیسیل ۷۵ ملی گرام ٹیبلیٹ

(کلوپیڈوگرل)

COMPOSITION:
Each film coated tablet contains:
Clopidogrel (as Bisulphate) .....75 mg
(USP Specifications)

DESCRIPTION
Clopisel (clopidogrel as sulphate) is an-inhibitor of ADP induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP mediated activation of the glycoprotein complex.

INDICATIONS:
Clopisel (clopidogrel as Sulphate) is indicated for the reduction of atherothrombotic events as follows:
Recent MI, Recent Stroke or Established Peripheral Arterial Disease
For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Clopisel has been shown to reduce the rate of a combined end point of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.
Acute Coronary Syndrome
For patients with acute coronary syndrome , including patients who are to be managed medically and those who are to be managed with perculaneous coronary intervention, Clopisel has been shown to decrease the rate of a combined end point of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

CLINICAL PHARMACOLOGY:
Mechanism of Action
Clopidogrel is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function in people with established atherosclerotic cardiovascular disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, or need for bypass angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate.
Pharmacokinetics and Metabolism
After repeated 75-mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.00025 mg/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 65% of the circulating drug-related compounds in plasma.
Following an oral dose of clopidogrel in human. approximately 50% was excreted in the urine and approximately 46% in the faces 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 Clopisel (clopidogrel as sulfate) with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.
Absorption and Distribution: Clopidogrel is rapidly absorbed after oral administration of repeated doses 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 concentrations increased in proportion to dose) in the 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 proteins (98% and 94%, respectively). The binding is nonsaturable in vitro up to a concentration of 100 ug/mL.
Metabolism and Elimination: in vitro and in vivo, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucouronide of the carboxylic acid derivative is also observed.

DOSAGE AND ADMINISTRATION
Recent MI, Recent Stroke, or Established Peripheral Arterial Disease
The recommended daily dose of Clopisel is 75 mg once daily.
Acute Coronary Syndrome
For Patients with acute coronary syndrome (unstable angina/non-O-wave MI), Clopisel should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with Clopisel. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely
Clopisel can be adminsitered with or without food.
No dosage adjustment is necessary for elderly patients or patients with renal disease.

CONTRAINDICATIONS
The use of Clopisel is contraindicated in the following conditions:
- Hypersensitivity to the drug substance or any component of the product.
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS & PRECAUTIONS:
Drugs Interactions
Study of specific drug interactions yielded the following results:
Aspirin:
Aspirin did not modify the clopidogrel - medicated inhibition of ADP induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the proiongation of bleeding time induced by Clopisel. Clopisel potentiated the effect of aspirin on collagen - induced platelet aggregation. The safety of chronic concomitant administration of aspirin and Clopisel has not been established.
Heparin:
In a study in healthy volunteers. Clopisel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by Clopisel. The safety of this combination has not been established. however, and concomilant use should be undertaken with caution.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):
In healthy volunteers receiving Naproxen, concomitant administration of Clopisel was associated with increased occult gastrointestinal blood loss. NSAIDs and Clopisel should be co administered with caution.
Warfarin:
The safety of the Coadministration of Clopisel (clopidogrel as sulphate) with warfarin has not been established. consequently, concomitant administration of these two agents should be undertaken with caution.
Other Concomitant Therapy:
No clinically significant pharmacodynamic interactions were observed when Clopisel was coadministered with Atenolol, Nifedipine, or both Atenolol and Nifedipine, The pharmacodynamic activity of Clopisel was also not significantly influenced by the Coadministration of phenobarbital & cimetidine.
The pharmacokinetics of digoxin or theophyline were not modified by the Coadministration of Clopisel (clopidogrel as sulphate).
At high concentrations in vitro, clopidogrel inhibits Ptso (2C9) Accordingly, Clopisel may interfere with the metabolism of Phenytoin Tamoxifen, Tolbutamide, Warfarin, Torsemide, Fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadminstered with Clopisel.
In addition to the above specific interaction studies, patients entered into Carrier received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents, antiepileptic agents and hormone replacement therapy without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility
There was no evidence of tumorigenicity when clopidogrel was adminsitered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures > 25 times that in humans at the recommended daily dose of 75 mg.
Clopidogrel was not genctoxic infour in vitro tests (Ames test, DNA- repair test in rat hepatocytes, gene mutation assay in Chinese
hamster fibroblasts, and metaphase chromosome analysis of human lymphocyter) and in one in vivo test (micronucleus test by oral route in mice).
Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m basis).
Pregnancy
Pregnancy Category B, Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 55 and 79 times the recommended daily human dose on a mg/nV 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 human response, Clopisel should be used during pregnancy only if clearly needed.
Nursing Mothers
Studies in rats have shown that clopidogrel and/or its metabolities 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.
Pediatric Use
Safety and affectiveness in the pediatric population have not been establishe.

WARNINGS:
Thrombotic thrombocytopenic purpura (TTP): TTP has been reported rarely following use of Clopisel, Sometimes after a short exposure (<2weeks). TTP is a serious condition requiring prompt treatment. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear). neurological finidings, 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 11cases per million patient-years, The background rate is thought to be about four cases per million person-years.

PRECAUTIONS:
General:
As with other anti-platelet agents, Clopisel should be used with caution in patients who may be at risk of increaed bleeding from trauma, surgery, or other pathological conditions. If a patient is to undergo elective surgery and an antiplatelet affect is not desired. Clopisel should be discontinued 7 days prior to surgery.
GI Bleeding: Clopisel prolongs the bleeding time. Clopisel was assiciated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. Clopisel should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce si ch lesions (such as aspirin and other nonsteroidal anti-inflammatory drugs [NASIDs] should be used with caution in patients taking Clopisel.
Use in Hepatcially impaired Patients: Experience is limited in patients with severe hepatic-disease, who may have bleeding . Clopisel should be used with caution in this population.

SIDE EFFECTS:
The most common side effects are nausea, vomiting, and diarrhea, The incidence of blood dyscrasias is lower with clopidogrel. Rare cases of thrombotic thrombocytopenic purpura have been associated with clopidogrel these usually remit when, the drug is stopped.
Side effects reported in clinical trials include (but are not limited to) the following:
- Pruritus (localized or generalized itching)
- Purpura (purple discoloring of the skin)
- Diarrhea
- Rash
- Neutropenia (decrease in white blood cells) is about 0.1%

OVER DOSAGE:
One case of deliberate overdosage with Clopisel was reported in the large, controlled clinical study. A 34-year old woman took a single 1.050 mg dose of Clopisel (equivalent to 14 standard 75mg tablets). There were no associated adverse events. No special therapy was instituted, and she recovered without single.
No adverse events were reported after signle oral administration of 600mg (equivalent to 8 standard 75mg tablets) of Clopisel in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75mg of Clopisel per day.
A single oral dose of clopidogrel at 1500 or 2000mg/kg was lethal to mice and to rats and at 3000mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.
Recommendations about specific treatment:
Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of Clopisel if quick reversal is required.

STORAGE & INSTRUCTIONS:
Store between 15-25°C.
Protect from heat, sunlight & moisture.
Keep away from the reach of children.
To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED:
Clopisel 75mg Tablet.
10's, 10x10's tablets.

خوراک وطریقہ استعمال:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:
دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔
دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Manufactured by:
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PRIVATE LIMITED
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120mm