CLOPI CI
Clopidogrel Tablets 75 mg

COMPOSITION:
Each film coated tabletcontains:
Clopidogrel Bisulphate
Eq. to Clopidogrel 75mg
Excipients q.s
Colour : Red oxide of iron

PHARMACODYNAMIC:
Pharmacotherapeutic group: Platelet aggregation inhibitors excl. heparin
ATC code: B01AC-04

Mechanism of actions:
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Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation.
Clopidogrel must be metabolised 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 P2Yl2 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/llla complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. 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 medicinal products, not all patients will have adequate platelet inhibition.

PHARMACOKINETIC:
Absoption:
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) occurred 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). The binding is non-saturable *in vitro* over a wide concentration range.

Biotransformation:
Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo,* clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised 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 metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4.
The active thiol metabolite which has been isolated *in vitro,* binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.
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 14C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.
Special populations
The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.
Renal impairment
After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease
(creatinine clearance from 5 to 15 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 perday. fu addition, clinical tolerance was good in all patients.
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. The mean bleeding time prolongation was also similar in the two groups.

INDICATION:
Prevention of atherothrombotic events
Clopidogrel is indicated in:
Adult patients suffering from myocardial infarction (from a few days until less than 35 days),
ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.
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 Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of
atherothrombotic and thromboembolic events, including stroke.

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
Adults and older people
Clopidogrel should be given as a single daily dose of 75 mg.
In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg.
Paediatric population
Clopidogrel should not be used in children because of efficacy concerns.
Renal impairment
Therapeutic experience is limited in patients with renal impairment.
Hepatic impairment
Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses.
Method of administration
For oral use
It may be given with or without food.

SPECIAL WARNING AND PRECAUTION FOR USE:
Before taking clopidogrel, tell your doctor or pharmacist if you are allergic to it; or to similar antiplatelet drugs (thienopyridines such as prasugrel); or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history, especially of: bleeding conditions (such as stomach ulcers, bleeding in the brain/eye), recent surgery, serious injury/trauma, liver disease, bleeding disease (such as hemophilia).

Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products). Your doctor may instruct you to stop clopidogrel for at least 5 days before surgery. Do not stop taking clopidogrel without talking with your heart doctor (cardiologist) first.

This medicine may cause stomach bleeding. Daily use of alcohol while using this medicine may increase your risk for stomach bleeding. Limit alcoholic beverages. Ask your doctor or pharmacist about how much alcohol you may safely drink.

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

INTERACTION WITH OTHER MEDICINE AND CONCOMITANT USE:
A product that may interact with this drug is: tipranavir.
If you are currently taking aspirin , consult your doctor promptly and ask whether to continue or stop taking it with this medication for your specific condition (aspirin and clopidogrel may be used in combination after a coronary stent procedure, or for some heart conditions). If you are not currently taking aspirin, consult your doctor before starting it for any medical condition.
Other medications can affect the removal of clopidogrel from your body, which may affect how clopidogrel works. Examples include certain acid reducers (proton pump inhibitors/PPIs such asomeprazole, esomeprazole), fluvoxamine, fluoxetine, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, and ticlopidine, among others.
Clopidogrel can slow down the removal of other drugs from your body, which may affect how they work. Examples of affected drugs include dasabuvir, repaglinide, among others.

PREGNACY AND LACTATION:
Pregnancy
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.
Breastfeeding
It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel.
Fertility
Clopidogrel was not shown to alter fertility in animal studies.

ADVERSE REACTION:

Although unlikely, serious bleeding in the stomach, gut, eyes, or brain may occur. Also, clopidogrel can rarely cause a very serious blood disorder (thrombotic thrombocytopenic purpura-TTP). Symptoms may appear any time after starting this medication. Symptoms include severe stomach/abdominal pain, uncontrolled bleeding from gums or nose, bloody/black stools, confusion, fever, extreme skin paleness, purple skin patches, fainting, fast heartbeat, sudden severe headache, unusual weakness/tiredness, vomit with blood or that looks like coffee grounds, slurred speech, vision changes, seizures, yellowing eyes/skin, bloody/red/pink/dark urine, signs of kidney problems (such as change in the amount of urine).
A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

This is not a complete list of possible side effects. If you notice other effects not listed above, contact your doctor or pharmacist.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Clopidogrel has no or negligible influence on the ability to drive and use machines.

OVERDOSE:
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.

INCOMPATIBILITY:
Not applicable

SHELF LIFE:
36 months

PACKAGING:
10 tablets are packed in one Alu Alu blister and such one blister is packed in a mono carton along with pack insert.

STORAGE CONDITION:
Store in a dry place below 30°C.

MANUFACTURED BY:
CIAN HEALTHCARE LTD.
(An ISO 9001 : 2015 & WHO GMP Certified Co.)
Kh. No. : 248, Village Sisona, Bhagwanpur, Roorkee,Haridwar, Uttarakhand, India.