PRESCRIBING INFORMATION
For the use of Registered medical Practitioner or a Hospital or a Laboratory

CLAVIX

(CLOPIDOGREL TABLETS USP 75 mg)

COMPOSITION
Each film coated tablet contains
Clopidogrel Bisulfate USP
equivalent to Clopidogrel ……75 mg

DESCRIPTION
Clopidogrel (Clavix) is an ADP receptor antagonist that is indicated for the reduction of atherosclerotic events including myocardial infarction, ischaemic stroke and vascular death in patients with atherosclerosis manifested by recent stroke, myocardial infarction or established peripheral vascular disease. It is one of the latest additions to the anti-platelet group of drugs. Various studies have demonstrated it to be superior to aspirin alone or to aspirin and ticlopidine combination. The tolerability of Clopidogrel is superior to aspirin and ticlopidine.
Chemically it is methyl (+)-(S)--(2-chlorophenyl)-6, 7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}Cl\,NO_2S{\cdot}H_2SO_4$ and its molecular weight is 419.9.

CLINICAL PHARMACOLOGY

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 atherosclerotic 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.

Pharmacodynamic Properties
Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.
Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.
Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Clavix. Repeated doses of 75 mg Clavix per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg Clavix per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

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 85% of the circulating drug-related compounds in plasma. 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 µg/ml.

Metabolism and Elimination
In vitro and in vivo, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

Special Population:
Geriatric Patients: No dosage adjustment is needed for the elderly.
Renally Impaired Patients: No dosage adjustment is needed for the renally impaired patients.

INDICATION
Clavix (Clopidogrel bisulfate) is indicated for the reduction of atherosclerotic events (myocardial infarction, stroke and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction or established peripheral arterial disease.

CONTRAINDICATION:
The use of Clavix 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.

PRECAUTIONS

General
As with other antiplatelet agents, Clavix prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, Clavix should be discontinued 7 days prior to surgery.
GI Bleeding:
Clavix prolongs the bleeding time. In CAPRIE, Clavix was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. Clavix 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 nonsteroidal anti-inflammatory drugs (NSAIDs)] should be used with caution in patients taking Clavix.
Use in Hepatically Impaired Patients:
Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Clavix should be used with caution in this population.

Carcinogenesis, Mutagenesis, Impairment of Fertility
There was no evidence of tumorigenicity when clopidogrel was administered 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 genotoxic in four in vitro tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) 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^2 basis).

Pregnancy
Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m^2 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 a human response, Clavix should be used during pregnancy only if clearly needed.

Nursing Mothers
Studies in rats have shown that clopidogrel and/or its metabolites 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 effectiveness in the pediatric population have not been established.

DOSE AND ADMINISTRATION
The recommded dose of Clavix 75 once daily with or without food. No dosage adjustment is necessary for elderly patients or patients with renal disease.

ADVERSE REACTIONS
Clavix has been evaluated for safety in more than 17,500 patients, including over 9,000 patients treated for 1 year or more. The overall tolerability of Clavix in CAPRIE was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. The clinically important adverse events observed in CAPRIE are:
Hemorrhagic
In patients receiving Clavix in CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for Clavix compared to 0.5% for aspirin.
Neutropenia/agranulocytosis
Ticlopidine, a drug chemically similar to Clavix, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/µL). Patients in CAPRIE were inteively monitored for neutropenia. Severe neutropenia was observed in six patients, four on Clavix and two on aspirin. Two of the 9599 patients who received Clavix and none of the 9586 patients who received aspirin had neutrophil counts of zero.
Gastrointestinal
Overall, the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving Clavix (clopidogrel bisulfate) was 27.1%, compared to 29.8% in those receiving aspirin.
The incidence of peptic, gastric or duodenal ulcers was 0.7% for Clavix and 1.2% for Aspirin.
Cases of diarrhea were reported in 4.5% of patients in the Clavix group compared to 3.4 % in the aspirin group. However, these were rarely severe (Clavix=0.2 % and aspirin= 0.1%).
Rash and other Skin Disorders: The incidence of skin and appendage disorders in patients receiving Clavix was 15.8% (0.7% serious); the corre, Pain, Fatigue, Asthenia, Hemia.
Cardiovascular disorders: Edema, Hypertension, Cardiac Failure.
Central and peripheral nervous system disorders: Headache, Dizziness, Cramps legs, Hypoaesthesia, Neuralgia, Paraesthasia, Vertigo.
Gastrointestinal System Disorders: Abdominal Pain, Dyspepsia, Diarrhea, Nausea, Constipation, Vomiting.
Heart Rate and Rhythm disorder: Atrial fibrillation.
Liver and billiary system disorders: Hepatic enzymes increased.
Metabolic and nutritional disorders: Arthragia, Back pain, Arthritis, Arthrosis, Platelet bleeding & clotting disorders: GI Hemorrhage, Hematoma, platelets decreased.
Psychiatric disorders: Depression, Anxiety, Insomnia.
Platelet, Bleeding and clotting Disorders: Purpura, Epistaxis.
Red blood cell disorder: Anemia.
Respiratory system disorder: Upper respiratory intection, Dyspnea, Rhinitis, Bronchitis, Coughing, Pneumonia, Sinusitis.
Skin and appendage disorders: Rash, Pruritis, Eczema, Skin ulceration.
Urinary System Disorders: Urinary tract infection, Cystitis.
Vision disorders: Cataract. Conjunctivitis.

Drug Interactions
Study of specific drug interactions yielded the following results:
Aspirin
Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by Clavix. Clavix potentiated the effect of aspirin on collagen-induced platelet aggregation.
Heparin
In a study in healthy volunteers, Clavix 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 Clavix. The safety of this combination has not been established, however, and concomitant use should be undertaken with caution.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
In healthy volunteers receiving naproxen, concomitant administration of Clavix was associated with increased occult gastrointestinal blood loss. NSAIDs and Clavix should be coadministered with caution.
Warfarin
The safety of the coadministration of Clavix with warfarin is 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 Clavix was coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of CLAVIX was also not significantly influenced by the coadministration of phenobarbital, cimetidine or estrogen.
At high concentrations in vitro, clopidogrel inhibits P450 (2C9). Accordingly, Clavix 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 coadministered with Clavix.

OVERDOSE
No adverse events were reported after single oral administration of 600 mg (equivalent to 8 standard 75-mg tablets) of Clavix 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 75 mg of Clavix per day.
A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/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 Clavix if quick reversal is required.

Storage:
Store in a cool dry place, protected from light.

Presentation:
Clavix Tablets are available in strips of 10 tablets.

Manufactured by :
INTAS
INTAS PHARMACEUTICALS LTD.
Matoda-382210, Dist. : Ahmedabad, INDIA
10 1723 1 658013
INP011

File Name: Clavix (658013)-Front
Size: 140 x 210 (mm)
Colour: Pan Black
Date: 10/11/2015

INTAS	Checked by			Approved by
	Packaging Dev.	Packaging Dev.	C.Q.A.	C.Q.A.
Signature				
Date				

File Name: Clavix (658013)-Back
Size: 140 x 210 (mm)
Colour: Pan Black
Date: 10/11/2015

INTAS	Checked by			Approved by
	Packaging Dev.	Packaging Dev.	C.Q.A.	C.Q.A.
Signature				
Date				