Norplat™ نورپلیٹ

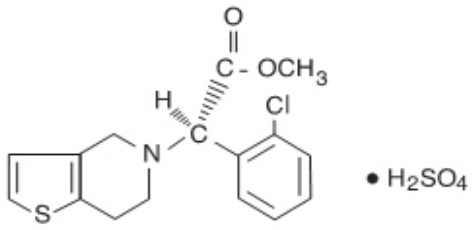
(Clopidogrel)

Tablets 75mg

DESCRIPTION

NORPLAT (Clopidogrel) is an inhibitor of ADP-induced platelet aggregation. It reduces the chance of having a heart attack or a stroke in people who have already had a heart attack or a stroke.

Chemically it is methyl (+)-(*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1). The molecular formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S.H_2SO_4$ and the structural formula is:



Clopidogrel bisulphate

QUALITATIVE & QUANTITATIVE COMPOSITION

NORPLAT (Clopidogrel) is available for oral administration as:

NORPLAT Tablets 75mg
Each film-coated tablet contains:
Clopidogrel...75mg
(as Clopidogrel bisulphate USP)

CLINICAL PHARMACOLOGY

Mechanism of Action

Clopidogrel is an inhibitor of platelet aggregation, that is, a drug that inhibits the ability of platelets to clump together as part of a blood.

It appears to act by blocking the adenosine phosphate (ADP) receptors, which prevents fibrinogen binding to the receptor. This decreases the ability of platelet adhesion and aggregation. Clopidogrel is a prodrug and requires biotransformation to produce inhibition of platelet aggregation. The active metabolite of clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP.

Pharmacokinetics

Clopidogrel after administration requires hepatic biotransformation to an active metabolite. Hepatic activation is thought to be mediated by the CYP P450 1A subfamily. The uncharacterized active metabolite is labile and highly reactive.

Absorption:

Following oral administration, clopidogrel is rapidly absorbed. Absorption is at least 50% and is not significantly affected by food. Peak plasma concentrations (roughly 3mg/l) of the primary circulating metabolite occur at about one hour following multiple dosing of 75mg/day. Plasma concentrations of the parent drug are undetectable 2 hours after an oral dose.

Distribution:

Clopidogrel and the main circulating metabolite bind reversibly to human plasma proteins (98% and 94%, respectively).

Metabolism:

Clopidogrel is extensively metabolized in the liver. The main circulating metabolite is the carboxylic acid derivative, and it has no effect on platelet aggregation. The active metabolite appears to be thiol derivative but has not been identified in plasma.

Elimination:

Clopidogrel and its metabolites are excreted about equally in urine and feces. The half-life of the carboxylic acid derivative is about 8 hours.

Special populations:

Renal Insufficiency

After repeated doses of 75mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15ml/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60ml/min) or healthy subjects. However, the prolongation of bleeding time was similar. No dose adjustment is required in mild to moderate renal impaired patients.

THERAPEUTIC INDICATIONS

- NORPLAT (Clopidogrel) is indicated for the reduction of thrombotic events in patients with recent myocardial infarction, recent stroke, or established peripheral arterial disease.
- NORPLAT (Clopidogrel) is used prophylactically in patients at risk of thromboembolic disorders such as myocardial infarction, peripheral arterial disease and stroke.
- NORPLAT (Clopidogrel) is also indicated for acute coronary syndrome (unstable angina/non-Q-wave MI).

DOSAGE AND ADMINISTRATION

NORPLAT (Clopidogrel) can be administered with or without food.

- *Recent MI, recent stroke, or established peripheral arterial disease:* The recommended daily dose is one NORPLAT tablet (75mg) daily.
- *Prophylactic use in patients at risk of thromboembolic disorders such as MI, peripheral arterial disease and stroke:* The recommended daily dose is one NORPLAT tablet (75mg) daily.
- *Acute coronary syndrome (unstable angina/non-Q-wave MI):* Dose should be initiated with a single 300mg-loading dose and then continued at 75mg once daily (with Aspirin 75mg-325mg once daily).

ADVERSE EFFECTS

Clopidogrel is generally well tolerated. However the following adverse effects have been reported during treatment.

Common: Gastrointestinal disturbances (Diarrhea, abdominal pain, indigestion and nausea) and dermatological reactions (rash, pruritis).
Less common: Chest pain, Nose bleeds.
Rare: Gastrointestinal bleeding, gastric ulcers, severe neutropenia or agranulocytosis, thrombocytopenia, thrombotic thrombocytopenic purpura, aplastic anemia, membranous nephropathy with nephrotic syndrome, loss of taste, acute arthritis.

CONTRAINDICATIONS

Clopidogrel is contraindicated in:

- Patients who have shown hypersensitivity to the drug or any component of the medication.
- Patients who suffer from active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

PRECAUTIONS

General

- 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, consideration should be given to stopping clopidogrel 5 days before surgery.
- Clopidogrel should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used in caution in patients taking clopidogrel.

Haematological

Clopidogrel should not be administered to patients with hematopoietic disorders such as neutropenia or thrombocytopenia, hemorrhagic diathesis or other hemorrhagic disorders associated with a prolonged bleeding time. Full blood count should be performed before starting treatment and every two weeks during the first three months of therapy. If clopidogrel is discontinued during this period, a full blood count should be performed within two weeks of stopping treatment.

Hepatic Impaired Patients

Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Clopidogrel should be used with caution in such patients.

Renal Impaired Patients

Experience is limited in patients with severe renal impairment. Clopidogrel should be used with caution in such patients.

Pediatric Use

Safety and effectiveness in the population have not been established.

Pregnancy

Clopidogrel has not been studied in pregnant women. It should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known if clopidogrel is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clopidogrel is given to a nursing mother.

Drug Interactions

Aspirin: A pharmacodynamic interaction between clopidogrel and aspirin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, clopidogrel and aspirin have been administered together for up to one year.

Heparin: A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken with caution.

Nonsteroidal 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.

Drugs metabolized by cytochrome P450:

At high concentrations *in vitro*, clopidogrel inhibits P450 (2C9). Accordingly, it 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 co-administered with clopidogrel.

STORAGE

Store below 30°C.
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

NORPLAT (Clopidogrel) Tablets 75mg are available in blister pack of 28's.

Keep out of reach of children.

Please read the contents carefully before use. This package insert is continually updated from time to time.

Manufactured by:
Getz Pharma (Pvt.) Limited, 29-30/27,
K.I.A., Karachi - 74900, Pakistan.

Marketed by:
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