Norplat-S™

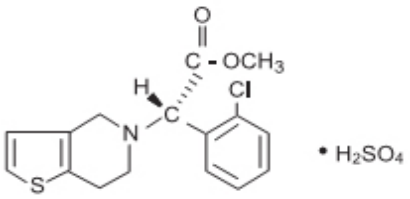
نورپلیٹ-ایس

(Clopidogrel+Aspirin)
75mg+75mg
Tablets

DESCRIPTION

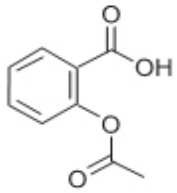
NORPLAT-S is a fixed-dose combination containing clopidogrel and aspirin.

Clopidogrel an inhibitor of platelet aggregation chemically described as methyl (+)-(*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2c]pyridine-5(4H)-acetate sulfate (1:1). The molecular formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S{\cdot}H_2SO_4$ the structural formula is:



Clopidogrel bisulphate

Aspirin also an anti-platelet agent and is chemically described as 2-(acetyloxy) benzoic acid. The molecular formula of aspirin is $C_9H_8O_4$ and the structural formula is:



Aspirin

QUALITATIVE & QUANTITATIVE COMPOSITION

NORPLAT-S (Clopidogrel+Aspirin) is available for oral administration as:

NORPLAT-S Tablets 75mg+75mg
Each double layered tablet contains:
Clopidogrel …75mg
(as Clopidogrel bisulphate USP)
Aspirin BP…75mg
(as enteric-coated tablet)

CLINICAL PHARMACOLOGY

Mechanism of Action

Clopidogrel:

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 clot.

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.

Aspirin:

Acetylsalicylic acid inhibits the activity of the enzyme cyclo-oxygenase and thus prostaglandins and thromboxane formation are decreased. By blocking thromboxane synthesis, acetylsalicylic acid inhibits rapidly the platelet aggregation; this action is irreversible. Acetylsalicylic acid may also inhibit formation of prostacyclin, a platelet aggregation inhibitor; this action is reversible.

Pharmacokinetics

Clopidogrel:

Clopidogrel is rapidly absorbed after oral administration. Absorption is at least 50%. It is a prodrug and is extensively metabolized in the liver, mainly to the inactive carboxylic acid derivative. The active metabolite appears to be a thiol derivative but has not been identified in plasma. Clopidogrel and the carboxylic acid derivatives are highly protein bound. Clopidogrel and its metabolites are excreted in urine and in feces. After oral administration, about 50% of a dose is recovered from the urine and about 46% from the faeces.

Aspirin:

After oral administration, absorption of aspirin occurs in the stomach and intestine. Once absorbed aspirin is rapidly converted to salicylate but during the first 20 minutes after a dose by mouth, aspirin is the predominant form of the drug in the plasma. Aspirin is 80 to 90% bound to plasma proteins and is widely distributed; its volume of distribution is reported to be 170 ml/kg in adults. As plasma-drug concentrations increase, the binding sites on the proteins become saturated and the volume of distribution increases. Both aspirin and salicylate have pharmacological activity although only aspirin has an anti-platelet effect. Salicylate appears in breast milk and crosses placenta and is mainly eliminated by hepatic metabolism. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption.

Special Populations:

Clopidogrel:

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

DOSAGE AND ADMINISTRATION

NORPLAT-S (Clopidogrel+Aspirin) can be administered with or without food.

The recommended dose is one tablet daily.

NORPLAT-S (Clopidogrel+Aspirin) has been administered for

up to one year.

ADVERSE EFFECTS

NORPLAT-S is generally well tolerated. However following are the few adverse effects reported during treatment.
Gastrointestinal disturbances: Diarrhea, abdominal pain, indigestion, nausea and heart burn.
Dermatological reactions: Rash, pruritus.
Ephritic ion reactions: Edema, urticaria, asthma.
Following adverse effects were reported rarely:
Increase bleeding tendency, gastrointestinal bleeding, gastric ulcers, severe neutropenia or agranulocytosis, thrombocytopenia, thrombotic thrombocytopenic purpura, aplastic anemia, membranous nephropathy with ephritic syndrome, loss of taste, acute arthritis.

CONTRAINDICATIONS

Clopidogrel+Aspirin combination is contraindicated in patients:

- Who have shown hypersensitivity to clopidogrel, aspirin or any component of the product.
- With active gastro-duodenal ulcers.
- With hypersensitivity to salicylates (bronchospasm, anaphylactic reactions).
- With haemorrhagic disease.
- With severe hepatic function impairment.
- Who are pregnant.
- Who are lactating.

PRECAUTIONS

Full blood count should be performed before starting treatment with clopidogrel+aspirin combination 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.

Aspirin should be used with caution in

- Children or teenagers with chickenpox, influenza or fever.
- Patients who are allergic to ibuprofen or other NSAID medicines.
- Patients with chronic or recurrent stomach or duodenal ulcers or digestive hemorrhages.
- Patients with severe renal disease.
- Patients suffering from allergic diseases like asthma or urticaria.
- Patients suffering from gout.

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.
- 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.

Hepatic Impaired Patients

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

Renal Impaired Patients

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

Drug Interactions

Anticoagulants, coumarin, heparin, or thrombolytic agents: Clopidogrel+Aspirin combination may cause hypoprothrombinaemia leading to increased anticoagulation and risk of bleeding when given concomitantly with anticoagulants, coumarin, heparin, or thrombolytic agents.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Concomitant administration of clopidogrel+aspirin combination may be associated with increased occult gastrointestinal blood loss. NSAIDs and clopidogrel+aspirin combination should be co-administered with caution.

Methotrexate: Aspirin may decrease renal clearance of methotrexate leading to toxic methotrexate plasma concentrations. If they are used concurrently, methotrexate dosage should be decreased.

Antidiabetic agents: Antidiabetic agents potentiate the effect of salicylates.

Uricosuric agents: Although salicylates in larger doses are uricosuric agents, smaller amounts may decrease the uricosuric effects of probencid, sulfinpyrazone and phenylbutazone.

Antacids: The effects of acetylsalicylic acid may be decreased by concurrent use of antacids.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken 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-S (Clopidogrel+Aspirin) Tablets 75mg+75mg are available in blister pack of 10'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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