Platrid™ 75mg Tablets
(Clopidogrel)

DESCRIPTION:
Platrid™ 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

COMPOSITION:
Platrid™ 75mg Tablets
Each film coated tablet contains:
Clopidogrel Bisulphate USP
equivalent to Clopidogrel.....75mg

CLINICAL PHARMACOLOGY:
Mechanism of Action
Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolized 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 P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GP IIb/IIIa 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

PHARMACOKINETICS:
Absorption: After single and repeated oral doses of 75mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites

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

Metabolism and Excretion: 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. 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

INDICATIONS:
- Adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease
- Adult patients suffering from acute coronary syndrome
- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
- ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.
- Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

DOSAGE AND ADMINISTRATION:
Recent MI, Recent Stroke, or Established Peripheral Arterial Disease
The recommended daily dose is 75mg once daily

Acute Coronary Syndrome
- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): Clopidogrel treatment should be initiated with a single 300mg loading dose and then continued at 75mg once a day
- ST segment elevation acute myocardial infarction: Clopidogrel should be given as a single daily dose of 75mg initiated with a 300mg loading dose in combination with ASA and with or without thrombolytics
  In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75mg

If a dose is missed:
- Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time
- For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose

ADVERSE REACTIONS:
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, pruritus)

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

OVERDOSAGE:
Overdose 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

CONTRAINDICATIONS:
Platrid™ is contraindicated in:
- Hypersensitivity to the drug substance or any component of the product
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage

WARNING & 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

DRUG INTERACTION:
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 nonsteroidal 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

USED IN SPECIAL POPULATION:
Pregnancy
Platrid™ has not been studied in pregnant women. It should be used during pregnancy only if clearly needed

Nursing Women: It is not known if **Platrid**™ 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

Pediatric Use: Safety and effectiveness in the population have not been established

Renal Impaired Patients: Experience is limited in patients with severe renal impairment. **Platrid**™ should be used with caution in such patients

Hepatic Impaired Patients: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Platrid should be used with caution in such patients

Hematological: **Platrid**™ 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

PRESENTATION:
Platrid™ 75mg tablets In a pack of 10's

INSTRUCTIONS:
Keep out of the reach of children
Avoid exposure to heat, light and humidity
Store between 15 to 30°C
Improper storage may deteriorate the medicine

پلیٹ رڈ™ ۷۵ ملی گرام ٹیبلٹ
(کلوپیڈوگرل)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

Platrid™-AP 75/75mg Tablets

(Clopidogrel + Aspirin)

DESCRIPTION:

Platrid™-AP is a combination of 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 and aspirin is an anti-platelet agent

COMPOSITION:

Platrid™-AP 75/75mg Tablets
Each film coated bi-layered tablet contains:
Clopidogrel Bisulphate USP
equivalent to Clopidogrel.....75mg
Aspirin USP (as enteric coated).....75mg

CLINICAL PHARMACOLOGY:

Mechanism of Action

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolized 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 P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa 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

Acetylsalicylic acid inhibits the activity of the enzyme cyclooxygenase 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

Absorption: After single and repeated oral doses of 75mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites

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

Metabolism and Excretion: 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. After a single oral dose of 75mg, 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

Aspirin:

Absorption: After oral administration, acetylsalicylic acid is rapidly absorbed from the gastrointestinal tract. However, a significant portion of the dosage is already hydrolyzed to salicylic acid in the intestinal wall during the absorption process

Distribution: Acetylsalicylic acid as well as the main metabolite salicylic acid, are extensively bound to plasma proteins, primarily albumin, and distributed rapidly into all parts of the body. Maximum plasma concentration is reached after 0.3 - 2 hours (total salicylate). The volume of distribution of acetylsalicylic acid is ca. 0.16 l/kg of body weight

Metabolism and Excretion: Salicylic acid and its metabolites are predominantly excreted via the kidneys

INDICATIONS:

- Adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease
- Adult patients suffering from acute coronary syndrome
- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (aspirin)
- ST segment elevation acute myocardial infarction, in combination with aspirin in medically treated patients eligible for thrombolytic therapy
- Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

DOSAGE AND ADMINISTRATION:

- Clopidogrel + aspirin can be administered with or without food
- Recent MI, Recent Stroke, or Established Peripheral Arterial Disease
- The recommended daily dose is 75mg once daily

Acute Coronary Syndrome:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): Clopidogrel treatment should be initiated with a single 300mg loading dose and then continued at 75mg once a day (with acetylsalicylic acid (aspirin) 75mg-325mg daily). Since higher doses of aspirin were associated with higher bleeding risk it is recommended that the dose of aspirin should not be higher than 100mg

- ST segment elevation acute myocardial infarction: Clopidogrel should be given as a single daily dose of 75mg initiated with a 300mg loading dose in combination with aspirin and with or without thrombolytics. For patients over 75 years of age clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks
- In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75mg. Aspirin (75-100mg daily) should be initiated and continued in combination with clopidogrel

If a dose is missed:

- Within less than 12 hours after regular scheduled time: Patients should take the dose immediately and then take the next dose at the regular scheduled time
- For more than 12 hours: Patients should take the next dose at the regular scheduled time and should not double the dose

OR

As directed by the physician

ADVERSE REACTIONS:

Clopidogrel + aspirin 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, pruritus)
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

OVERDOSAGE:

Overdose administration may lead to prolonged bleeding time and subsequent bleeding complications

CONTRAINDICATIONS:

Clopidogrel + aspirin is contraindicated in:

- Hypersensitivity to the drug substance or any component of the product
- Severe hepatic impairment
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage

WARNINGS & PRECAUTIONS:
General:
- Clopidogrel + aspirin 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 + aspirin 5 days before surgery
- Clopidogrel + aspirin 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 + aspirin

DRUG INTERACTION:
Aspirin: A pharmacodynamic interaction between clopidogrel + aspirin is possible, leading to increased risk of bleeding. Therefore; concomitant use should be undertaken with caution. However, clopidogrel + 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 nonsteroidal 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

Antacids: The excretion of acetylsalicylic acid is increased by alkaline urine, which can occur with some antacids

Antidiabetic agents: Antidiabetic agents potentiate the effect of salicylates

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

Alcohol: Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding

USED IN SPECIAL POPULATION:
Pregnancy: **Platrid™-AP** should not be used during first two trimesters unless the clinical condition of the woman requires treatment with **Platrid™-AP**. It is contraindicated during third trimester of pregnancy

Nursing Women: **Platrid™-AP** should be avoided in nursing mother because of the possible risk of developing Reye's syndrome or breastfeeding should be discontinued during treatment with **Platrid™-AP**

Paediatric Use: Safety and effectiveness in the population have not been established

Renal Impaired Patients: Experience is limited in patients with severe renal impairment. **Platrid™-AP** should be used with caution in such patients

Hepatic Impaired Patients: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses
Platrid™-AP should be used with caution in such patients

STABILITY:
See expiry on the pack

PRESENTATION:
Platrid™-AP 75/75mg tablets in a pack of 10's

INSTRUCTIONS:
Keep out of the reach of children
Avoid exposure to heat, light and humidity
Store between 15 to 30 °C
Improper storage may deteriorate the medicine

پلیٹ رڈ™-اے پی ۷۵/۷۵ ملی گرام ٹیبلٹ

(کلوپیڈوگرل + اسپرین)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com