**Summary of Product Characteristics**

# Platrid® Tablet

# Platrid®-AP Tablet

# Platrid®
(Clopidogrel)

## 1. NAME OF THE PRODUCT
**Platrid®** (Clopidogrel) 75mg Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
**Platrid® 75mg Tablets**
Each film coated tablet contains:
Clopidogrel Bisulphate USP equivalent to Clopidogrel…....75mg

## 3. PHARMACEUTICAL FORM
Film-coated tablet

**Appearance:** Light pink to pink round tablet, plain from both sides.

## 4. CLINICAL PARTICULARS
### 4.1. THERAPEUTIC INDICATIONS:
**Secondary prevention of atherothrombotic events:**
**Platrid®** is indicated in:

- Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischemic stroke (from 7 days until less than 6 months) 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 aspirin.
  - ST segment elevation acute myocardial infarction, in combination with aspirin in patients undergoing percutaneous coronary intervention (including patients undergoing a stent placement) or medically treated patients eligible for thrombolytic/fibrinolytic therapy.

**In patients with moderate to high-risk transient ischemic attack (TIA) or minor ischemic stroke (IS):**
Clopidogrel in combination with aspirin is indicated in:

- Adult patients with moderate to high-risk TIA (ABCD2[1] score ≥4) or minor IS (NIHSS[2] ≤3) within 24 hours of either the TIA or IS event.

**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 aspirin for the prevention of atherothrombotic and thromboembolic events, including stroke.

[1]Age, blood pressure, clinical features, duration and diabetes mellitus diagnosis.

[2]National institutes of health stroke scale.

## 4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

**Posology:**

**Adults and elderly: Platrid®** should be given as a single daily dose of 75mg.

**In patients suffering from 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 or 600mg loading dose. A 600mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended. Clopidogrel treatment should be continued at 75mg once a day (with 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. The optimal duration of treatment has not been formally established.

***ST segment elevation acute myocardial infarction:*** For medically treated patients eligible for thrombolytic/fibrinolytic therapy, 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 medically treated 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. The benefit of the combination of clopidogrel with aspirin beyond four weeks has not been studied.

***When percutaneous coronary intervention (PCI) is intended:*** Clopidogrel should be initiated at a loading dose of 600mg in patients undergoing primary PCI and in patients undergoing PCI more than 24 hours of receiving fibrinolytic therapy. In patients ≥75 years old the 600mg LD should be administered with caution. Clopidogrel 300mg loading dose should be given in patients undergoing PCI within 24 hours of receiving fibrinolytic therapy. Clopidogrel treatment should be continued at 75mg once a day with aspirin 75mg – 100mg daily. Combined therapy should be started as early as possible after symptoms start and continued up to 12 months.

**Adult patients with moderate to high-risk TIA or minor IS:**

Adult patients with moderate to high-risk TIA (ABCD2 score ≥4) or minor IS (NIHSS ≤3) should be given a loading dose of clopidogrel 300mg followed by clopidogrel 75mg once daily and aspirin (75mg -100mg once daily). Treatment with clopidogrel and aspirin should be started within 24 hours of the event and be continued for 21 days followed by single antiplatelet therapy. 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.

**Special populations:**
**Elderly patients:**
***Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction):***

- A 600mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended.

***ST segment elevation acute myocardial infarction:***

- For medically treated patients eligible for thrombolytic/fibrinolytic therapy: in patients over 75 years of age clopidogrel should be initiated without a loading dose.

***For patients undergoing primary PCI and in patients undergoing PCI more than 24 hours of receiving fibrinolytic therapy:***

- In patients ≥75 years old the 600mg LD should be administered with caution.

**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:**
**Platrid®** is intended for oral use.
It may be given with or without food.

## 4.3. CONTRAINDICATIONS:

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

## 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

**Bleeding and haematological disorders:** Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment. As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with aspirin, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers or other medicinal products associated with bleeding risk such as pentoxifylline. Due to the increased risk of haemorrhage, triple antiplatelet therapy (clopidogrel + aspirin + dipyridamole) for stroke secondary prevention is not recommended in patients with acute non-cardioembolic ischemic stroke or TIA. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings. If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular). Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with aspirin), and that they should report any unusual bleeding (site or duration) to their physician. The use of clopidogrel 600mg loading dose is not recommended in patients with non-ST segment elevation acute coronary syndrome and ≥75 years of age due to increased bleeding risk in this population. Due to the limited clinical data in patients ≥75 years old with STEMI PCI, and increased risk of bleeding, the use of clopidogrel 600mg loading dose should be considered only after an individual assessment of the bleeding risk of the patient by the physician.

**Thrombotic thrombocytopaenic purpura (TTP):** Thrombotic Thrombocytopaenic purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterized by thrombocytopaenia and microangiopathic haemolytic anaemia associated with either neurological finding, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

**Acquired haemophilia:** Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated partial thromboplastin time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia

should be managed and treated by specialists, and clopidogrel should be discontinued.

**Recent ischemic stroke:**

- ***Initiation of therapy:*** In acute minor IS or moderate to high-risk TIA patients, dual antiplatelet therapy (clopidogrel and aspirin) should be started no later than 24 hours after the event onset. There is no data regarding the benefit-risk of short term dual antiplatelet therapy in acute minor IS or moderate to high-risk TIA patients, with a history of (non-traumatic) intracranial haemorrhage. In non-minor IS patients, clopidogrel monotherapy should be started only after the first 7 days of the event.
- ***Non-minor IS patients (NIHSS >4):*** In view of the lack of data, use of dual antiplatelet therapy is not recommended.
- ***Recent minor IS or moderate to high-risk TIA in patients for whom intervention is indicated or planned:*** There is no data to support the use of dual antiplatelet therapy in patients for whom treatment with carotid endarterectomy or intravascular thrombectomy is indicated, or in patients planned for thrombolysis or anticoagulant therapy. Dual antiplatelet therapy is not recommended in these situations.

**Cytochrome P450 2C19 (CYP2C19):**

***Pharmacogenetics:*** In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype. Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. Use of medicinal products that induce the activity of CYP2C19 would be expected to result in increased drug levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution concomitant use of strong or moderate CYP2C19 inducers should be discourage.

**CYP2C8 substrates:** Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products.

**Cross-reactions among thienopyridines:** Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported. Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

**Renal impairment:** Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore, clopidogrel should be used with caution in these patients.

**Hepatic impairment:** Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population.

**Excipients:** This medicinal product contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

## 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

**Medicinal products associated with bleeding risk:** There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution.

**Oral anticoagulants:** The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings. Although the administration of clopidogrel 75mg/day did not modify the pharmacokinetics of S-warfarin or International Normalized Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on haemostasis.

**Glycoprotein IIb/IIIa inhibitors:** Clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors.

**Aspirin:** Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregation. 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:** Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

**Thrombolytics:** The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with aspirin.

**NSAIDs:** The concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution.

**SSRIs:** Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

**Other concomitant therapy:**

**Inducers of CYP2C19:** Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that induce the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel. Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged.

**Inhibitors of CYP2C19:** Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged. Medicinal products that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.

**Proton pump inhibitors (PPI):** Omeprazole 80mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel. Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole. The plasma concentrations of the active metabolite was 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole. There is no evidence that other medicinal products that reduce stomach acid such as $H_2$ blockers or antacids interfere with antiplatelet activity of clopidogrel.

**Boosted anti-retroviral therapy (ART):** HIV patients treated with boosted anti-retroviral therapies (ART) are at high-risk of vascular events. A significantly reduced platelet inhibition has been shown in HIV patients treated with ritonavir- or cobicistat-boosted ART. Average platelet inhibition can be decreased with concomitant use of clopidogrel and ritonavir. Therefore, concomitant use of clopidogrel with ART boosted therapies should be discouraged.

**Other medicinal products:** No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen. The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

**CYP2C8 substrate medicinal products:** *In vitro* studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma 9 concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution. As with other oral P2Y12 inhibitors, co-administration of opioid agonists has the potential to delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying. The clinical relevance is unknown. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

**Rosuvastatin:** Clopidogrel has been shown to increase rosuvastatin exposure in patients by 2-fold (AUC) and 1.3-fold ($C_{max}$) after administration of a 300mg clopidogrel dose, and by 1.4-fold (AUC) without effect on $C_{max}$ after repeated administration of a 75mg clopidogrel dose.

## 4.6. FERTILITY, PREGNANCY AND LACTATION:

**Fertility:** Clopidogrel was not shown to alter fertility in animal studies.

**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.

**Breast-feeding:** It is unknown whether clopidogrel is excreted in human breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel.

## 4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Clopidogrel has no or negligible influence on the ability to drive and use machines.

## 4.8. UNDESIRABLE EFFECTS:

Adverse reactions that were spontaneously reported are presented below. Their frequency is defined using the following conventions: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

**Blood and lymphatic system disorders:**
***Uncommon:*** Thrombocytopenia, leucopenia, eosinophilia
***Rare:*** Neutropenia, including severe neutropenia
***Very rare/ Not known:*** Thrombotic thrombocytopenic purpura (TTP), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia
**Immune system disorders:**
***Very rare/ Not known:*** Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel), insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)*
**Psychiatric disorders:**
***Very rare/ Not known:*** Hallucinations, confusion
**Nervous system disorders:**
***Uncommon:*** Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness
***Very rare/ Not known:*** Taste disturbances, ageusia
**Eye disorders:**
***Uncommon:*** Eye bleeding (conjunctival, ocular, retinal)
**Cardiac disorders:**
***Very rare/ Not known:*** Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel*
**Vascular disorders:**
***Common:*** Haematoma
***Very rare/ Not known:*** Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
**Ear and labyrinth disorders:**
***Rare:*** Vertigo
**Respiratory, thoracic and mediastinal disorders:**
***Common:*** Epistaxis
***Very rare/ Not known:*** Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
**Gastrointestinal disorders:**
***Common:*** Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia
***Uncommon:*** Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence
***Rare:*** Retroperitoneal haemorrhage
**Very rare/ Not known:** Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis

**Hepato-biliary disorders:**
***Very rare/ Not known:*** Acute liver failure, hepatitis, abnormal liver function test
**Skin and subcutaneous tissues disorders:**
***Common:*** Bruising
***Uncommon:*** Rash, pruritus, skin bleeding (purpura)
***Very rare/ Not known:*** Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme, acute generalized exanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus.
**Reproductive system and breast disorders:**
***Rare:*** Gynaecomastia
**Musculoskeletal, connective tissue and bone disorders:**
***Very rare/ Not known:*** Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
**Renal and urinary disorders:**
***Uncommon:*** Haematuria
***Very rare/ Not known:*** Glomerulonephritis, blood creatinine increased
**General disorders and administration site conditions:**
***Common:*** Bleeding at puncture site
***Very rare/Not known:*** Fever
**Investigations:**
***Uncommon:*** Bleeding time prolonged, neutrophil count decreased; platelet count decreased
* Information related to clopidogrel with frequency “not known”.

### 4.9. 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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. PHARMACODYNAMIC PROPERTIES:

**Pharmacotherapeutic group:** Platelet aggregation inhibitors excl. heparin, **ATC Code:** B01AC-04.
Repeated doses of 75mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75mg per day was between 40% and

60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

**Mechanism of action:** 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 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. 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.

## 5.2. PHARMACOKINETICS PROPERTIES:

**Absorption:** After single and repeated oral doses of 75mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5ng/ml after a single 75mg 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 $C_{max}$ of the active metabolite is twice as high following a single 300mg clopidogrel loading dose as it is after four days of 75mg maintenance dose. $C_{max}$ occurs approximately 30 to 60 minutes after dosing.

**Elimination:** Following an oral dose of $^{14}C$-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 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.

### 5.3. PRECLINICAL SAFETY DATA:

During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose. At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon. There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75mg/day). Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity. Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. LIST OF EXCIPIENTS:

**Excipients:**

- Microcrystalline Cellulose
- Lactose Monohydrate
- Crospovidone
- Hydroxypropyl Cellulose
- Silicon Dioxide Fumed
- Magnesium Stearate
- Castor Oil Hydrogenated

**Materials for film coating:**

- Sheffcoat
- Red Iron Oxide Color
- Purified water

### 6.2. INCOMPATIBILITIES:
Not applicable

### 6.3. SHELF LIFE:
See expiry on the pack.

### 6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Store between 15 to 30°C
Improper storage may deteriorate the medicine.
Keep out of reach of children.

### 6.5. NATURE AND CONTENTS OF CONTAINER:
Alu/Alu blister, pack size is 10's.

### 6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
No special requirements for disposal.

### 6.7. DRUG PRODUCT SPECIFICATIONS:
USP Specs.

## 7. REGISTRATION / MARKETING AUTHORISATION HOLDER
Manufactured by:
**SAMI Pharmaceuticals (Pvt.) Ltd.**
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

## 8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)
036345

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
31st December, 2004

## 10. DATE OF REVISION OF THE TEXT

# پلیٹ رڈ® ٹیبلٹ

(کلو پیڈ وگرل)

## ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت 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۔

# Platrid®-AP

**(Clopidogrel + Aspirin)**

## 1. NAME OF THE PRODUCT

**Platrid®-AP** (Clopidogrel + Aspirin) 75/75mg Tablets

## 2. QUALITATIVE AND QUANTITATIVE 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

## 3. PHARMACEUTICAL FORM

Film-coated tablet

**Appearance:** Yellow color, round shape enteric coated tablets plain on both sides.

## 4. CLINICAL PARTICULARS

### 4.1. THERAPEUTIC INDICATIONS:

**Platrid®-AP** is indicated for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and aspirin. **Platrid®-AP** is a fixed-dose combination medicinal product for continuation of therapy in:

- 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.
- ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy.

### 4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

**Posology:**

**Adults and Elderly: Platrid®-AP** should be given as a single daily 75mg/75mg dose.

**Platrid®-AP** fixed-dose combination is used following initiation of therapy with clopidogrel and aspirin given separately, and replaces the individual clopidogrel and aspirin products.

- **In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction):** The optimal duration of treatment has not been formally established. Clinical trial data

support use up to 12 months, and the maximum benefit was seen at 3 months. If the use of **Platrid®-AP** is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

- **In patients with ST segment elevation acute myocardial infarction:** Therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with aspirin beyond four weeks has not been studied in this setting. If the use of **Platrid®-AP** is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

**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.

**Paediatric population:** The safety and efficacy of Clopidogrel/Aspirin in children and adolescents under 18 years old have not been established. Clopidogrel/Aspirin acid is not recommended in this population.
**Renal impairment:** Clopidogrel/Aspirin must not be used in patients with severe renal impairment. Therapeutic experience is limited in patients with mild to moderate renal impairment. Therefore Clopidogrel/Aspirin should be used with caution in these patients.
**Hepatic impairment:** Clopidogrel/Aspirin must not be used in patients with severe hepatic impairment. Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Therefore Clopidogrel/Aspirin should be used with caution in these patients.

**Method of administration:**
For oral use. It may be given with or without food.

## 4.3. CONTRAINDICATIONS:

Due to the presence of both components of the medicinal product, Clopidogrel/Aspirin is contraindicated in case of:

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

In addition, due to the presence of aspirin, its use is also contraindicated in:

- Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and syndrome of asthma, rhinitis, and nasal polyps. Patients with pre-existing mastocytosis, in whom the use of aspirin may induce severe hypersensitivity

reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting).

- Severe renal impairment (creatinine clearance<30ml/min).
- Third trimester of pregnancy

## 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

**Bleeding and haematological disorders:** Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment. As a dual antiplatelet agent, Clopidogrel/ Aspirin should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with other NSAIDs including COX-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), CYP2C19 strong inducers, thrombolytics, or other medicinal products associated with bleeding risk such as pentoxifylline. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of Clopidogrel/Aspirin with oral anticoagulants is not recommended since it may increase the intensity of bleeding. Patients should inform physicians and dentists that they are taking Clopidogrel/Aspirin before any surgery is scheduled and before any new medicinal product is taken. Where elective surgery is being considered, the need for dual antiplatelet therapy should be reviewed and consideration given to the use of a single antiplatelet agent. Clopidogrel/Aspirin prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular). Patients should also be told that it might take longer than usual to stop bleeding when they take Clopidogrel/Aspirin, and that they should report any unusual bleeding (site or duration) to their physician.

**Thrombotic Thrombocytopaenic Purpura (TTP):** Thrombotic Thrombocytopaenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterized by thrombocytopaenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

**Acquired haemophilia:** Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

**Recent transient ischaemic attack or stroke:** In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of aspirin and clopidogrel has been shown to increase major bleeding. Therefore, such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

**Cytochrome P450 2C19 (CYP2C19):** Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype. Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged.

**CYP2C8 substrates:** Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products.

**Cross-reactions among thienopyridines:** Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported. Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

**Caution required due to Aspirin:**

- In patients with a history of asthma or allergic disorders since they are at increased risk of hypersensitivity reactions.
- In patients with gout since low doses of aspirin increase urate concentrations.
- In children under 18 years of age, there is a possible association between aspirin and Reye’s syndrome. Reye’s syndrome is a very rare disease which can be fatal.
- This medicinal product must be administered under close medical supervision in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to risk of haemolysis.
- Alcohol may increase the risk of gastrointestinal injury when taken with aspirin. Patients should be counselled about the risks of gastrointestinal injury and bleeding while taking clopidogrel plus aspirin with alcohol, especially if alcohol consumption is chronic or heavy.

**Gastrointestinal (GI):** Clopidogrel/ Aspirin should be used with caution in patients with a history of peptic ulcer or gastroduodenal haemorrhage or minor upper GI symptoms as this may be due to gastric ulceration which may lead to gastric bleeding. GI undesirable effects including stomach pain, heartburn, nausea, vomiting, and GI bleeding may occur. Minor GI symptoms, such as dyspepsia, are common and can occur anytime during therapy. Physicians should remain alert for signs of GI ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be told about the signs and symptoms of GI undesirable effects and what steps to take if they occur. In patients concomitantly receiving nicorandil and NSAIDs including aspirin and LAS, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage.

**Excipients:** Clopidogrel/ Aspirin contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. This medicinal product also contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

## 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

**Medicinal products associated with bleeding risk:** There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution.

**Oral anticoagulants:** The concomitant administration of Clopidogrel/Aspirin with oral anticoagulants is not recommended since it may increase the intensity of bleeding. Although the administration of clopidogrel 75mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on haemostasis.

**Glycoprotein IIb/IIIa inhibitors:** Clopidogrel/Aspirin should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors.

**Heparin:** Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between Clopidogrel/Aspirin and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

**Thrombolytics:** The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The safety of the concomitant administration of Clopidogrel/Aspirin with other thrombolytic agents has not been formally established and should be undertaken with caution.

**NSAIDs:** The concomitant use of NSAIDs including COX-2 inhibitors is not recommended.
**Metamizole:** Metamizole may reduce the effect of aspirin on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardio protection.
**SSRIs:** Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

**Other concomitant therapy with clopidogrel:**
**Inducers of CYP2C19:** Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel. Rifampicin strongly induces CYP2C19 resulting to both an increase level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged.
**Inhibitors of CYP2C19:** Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. Medicinal products that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.
**Proton Pump Inhibitors (PPI):** Omeprazole 80mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel. There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.
**Anti-retroviral therapies (ART):** A significantly lower exposure to clopidogrel active metabolite and reduced platelet inhibition have been demonstrated in HIV-infected patients treated with ritonavir- or cobicistat-boosted anti-retroviral therapies. Exposure of clopidogrel and average platelet inhibition can be decreased with concomitant use of ritonavir. Therefore, concomitant use of clopidogrel with boosted ART should be discouraged.
**Other medicinal products:** No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the

co-administration of phenobarbital or oestrogen. The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

**CYP2C8 substrate medicinal products:** Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.

**Other concomitant therapy with Aspirin:**

Interactions with the following medicinal products have been reported with Aspirin:

**Uricosurics (benzbromarone, probenecid, sulfinpyrazone):** Caution is required because aspirin may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

**Methotrexate:** Due to the presence of aspirin, methotrexate used at doses higher than 20mg/week should be used with caution with Clopidogrel/ Aspirin as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

**Tenofovir:** Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.

**Valproic acid:** The concomitant administration of salicylates and valproic acid may result in decreased valproic acid protein binding and inhibition of valproic acid metabolism resulting in increased serum levels of total and free valproic acid.

**Varicella vaccine:** It is recommended that patients not be given salicylates for an interval of six weeks after receiving the varicella vaccine. Cases of Reye's syndrome have occurred following the use of salicylates during varicella infections.

**Acetazolamide:** Caution is recommended when co-administering salicylates with acetazolamide as there is an increased risk of metabolic acidosis.

**Nicorandil**: In patients concomitantly receiving nicorandil and NSAIDs including aspirin and LAS, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage.

**Other interactions with Aspirin:** Interactions with the following medicinal products with higher (anti-inflammatory) doses of aspirin have also been reported: angiotensin converting enzyme (ACE) inhibitors, phenytoin, beta-blockers, diuretics, and oral hypoglycaemic agents.

**Alcohol:** Alcohol may increase the risk of gastrointestinal injury when taken with aspirin. Patients should be counselled about the risks of gastrointestinal injury and bleeding while taking clopidogrel plus aspirin with alcohol, especially if alcohol consumption is chronic or heavy.

**Other interactions with clopidogrel and Aspirin:** Clopidogrel/Aspirin and some medicinal products commonly administered in patients with

atherothrombotic disease have not been performed. As with other oral P2Y12 inhibitors, co-administration of opioid agonists has the potential to delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying. The clinical relevance is unknown. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

## 4.6. FERTILITY, PREGNANCY AND LACTATION:

**Fertility:** There are no fertility data with Clopidogrel/ Aspirin. It is unknown whether aspirin dose in Clopidogrel/ Aspirin alters fertility.

**Pregnancy:** Clopidogrel/ Aspirin should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with Clopidogrel/ Aspirin. Due to the presence of aspirin, Clopidogrel/ Aspirin is contraindicated during the third trimester of pregnancy.

**Breast-feeding:** It is unknown whether clopidogrel is excreted in human breast milk. Aspirin is known to be excreted in limited amounts in human milk. Breast-feeding should be discontinued during treatment with Clopidogrel/ Aspirin.

## 4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Clopidogrel/ Aspirin has no or negligible influence on the ability to drive and use machines.

## 4.8. UNDESIRABLE EFFECTS:

Adverse reactions that occurred with clopidogrel alone, with aspirin alone or with clopidogrel in combination with aspirin were spontaneously reported are presented below. Their frequency is defined using the following conventions: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

**Blood and Lymphatic system disorders:**

***Uncommon:*** Thrombocytopenia, leucopenia, eosinophilia.

***Rare:*** Neutropenia, including severe neutropenia.

***Very rare/ Not known:*** Thrombotic thrombocytopenic purpura (TTP), bone marrow failure*, aplastic anaemia, pancytopenia, bicytopenia*, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia, haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency*.

**Immune system disorders:**

***Very rare/ Not known:*** Anaphylactic shock*, serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel), insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with HLA DRA4 subtype (more frequent

in the Japanese population) **, aggravation of allergic symptoms of food allergy*.

**Metabolism and Nutrition disorders:**

***Very rare/ Not known:*** Hypoglycaemia*, gout*.

**Psychiatric disorders:**

***Very rare/ Not known:*** Hallucinations, confusion.

**Nervous system disorders:**

***Uncommon:*** Intracranial bleeding (some cases were reported with fatal outcome, especially in elderly), headache, paraesthesia, dizziness.

***Very rare/ Not known:*** Taste disturbances, ageusia.

**Eye disorders:**

***Uncommon:*** Eye bleeding (conjunctival, ocular, retinal).

**Ear and Labyrinth disorders:**

***Rare:*** Vertigo.

***Very rare/ Not known:*** Hearing loss* or tinnitus*.

**Cardiac disorders:**

***Very rare/ Not known:*** Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to aspirin* or clopidogrel**.

**Vascular disorders:**

***Common:*** Haematoma.

***Very rare/ Not known:*** Serious haemorrhage, haemorrhage of operative wound, vasculitis (including Henoch-Schönlein purpura*), hypotension.

**Respiratory, thoracic and mediastinal disorders:**

***Common:*** Epistaxis.

***Very rare/ Not known:*** Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, non-cardiogenic pulmonary oedema with chronic use and in the context of a hypersensitivity reaction due to aspirin*, eosinophilic pneumonia.

**Gastrointestinal disorders:**

***Common:*** Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia.

***Uncommon:*** Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence.

***Rare:*** Retroperitoneal haemorrhage.

***Very rare/ Not known:*** Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis. Upper gastrointestinal disorders (oesophagitis, oesophageal ulceration, perforation, erosive gastritis, erosive duodenitis; gastro-duodenal ulcer/perforations)*, lower gastrointestinal disorders (small [jejunum and ileum] and large [colon and rectum] intestinal ulcers, colitis and intestinal perforation)*; upper gastro-intestinal symptoms* such as gastralgia, these aspirin related GI reactions may or may not be associated with haemorrhage, and may occur at any dose of aspirin and in patients with or

without warning symptoms or a previous history of serious GI events*. Colitis (including ulcerative or lymphocytic colitis), stomatitis, acute pancreatitis in the context of a hypersensitivity reaction due to aspirin*.

**Hepatobiliary disorders:**

***Very rare/ Not known:*** Acute liver failure, liver injury, mainly hepatocellular*, hepatitis, elevation of hepatic enzymes*, abnormal liver function test, chronic hepatitis*.

**Skin and Subcutaneous tissues disorders:**

***Common:*** Bruising.

***Uncommon:*** Rash, pruritus, skin bleeding (purpura).

***Very rare/ Not known:*** Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus, fixed eruption*.

**Reproductive systems and Breast disorders:**

***Rare:*** Gynaecomastia.

**Musculoskeletal and Connective tissue disorders:**

***Very rare/ Not known:*** Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia.

**Renal and Urinary disorders:**

***Uncommon:*** Haematuria.

***Very rare/ Not known:*** Renal failure*, acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics) *, glomerulonephritis, blood creatinine increased.

**General disorders and administration site conditions:**

***Common:*** Bleeding at the puncture site.

***Very rare/ Not known:*** Fever, oedema*.

**Investigations:**

***Uncommon:*** Bleeding time prolonged, neutrophil count decreased; platelet count decreased.

* Information reported in published information for aspirin with frequency “not known”.

** Information related to clopidogrel with frequency “not known”.

## 4.9. OVERDOSE

**Clopidogrel:**

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.

**Aspirin:**

The following symptoms are associated with moderate intoxication: dizziness, headache, tinnitus, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain). With severe intoxication, serious disturbances of the acid-base equilibrium occur. Initial hyperventilation leads to respiratory alkalosis. Subsequently a respiratory acidosis occurs as a result of a suppressive effect on the respiratory center. A metabolic acidosis also arises due to the presence of salicylates. Given that children, infants and toddlers are often only seen at a late stage of intoxication, they will usually have already reached the acidosis stage. The following symptoms can also arise: hyperthermia and perspiration, leading to dehydration, restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system can lead to coma, cardiovascular collapse and respiratory arrest. The lethal dose of aspirin is 25-30g. Plasma salicylate concentrations above 300mg/l (1.67mmol/l) suggest intoxication. Overdose with Aspirin/clopidogrel fixed dose combination may be associated with increased bleeding and subsequent bleeding complications due to the pharmacological activity of clopidogrel and aspirin. Non-cardiogenic pulmonary oedema can occur with acute and chronic aspirin overdose. If a toxic dose has been ingested then admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting; if this fails, gastric lavage is indicated. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalising of the urine (250mmol sodium bicarbonate for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1. PHARMACODYNAMIC PROPERTIES:

**Pharmacotherapeutic group:** Antithrombotic agents, platelet aggregation inhibitors excl. Heparin.

**ATC Code:** B01AC30.

**Mechanism of action:** 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 $P2Y_{12}$ 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. 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.
Aspirin inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane $A_2$ an inducer of platelet aggregation and vasoconstriction. This effect last for the life of the platelet.

## 5.2. PHARMACOKINETICS PROPERTIES:

**Clopidogrel:**

**Absorption:** After single and repeated oral doses of 75mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5ng/ml after a single 75mg 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. 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 $C_{max}$ of the active metabolite is twice as high following a single 300mg clopidogrel loading dose as it is after four days of 75mg maintenance dose. $C_{max}$ occurs approximately 30 to 60 minutes after dosing.
**Elimination:** Following an oral dose of $^{14}C$-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 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**: Following absorption, the aspirin in Clopidogrel/Aspirin is hydrolysed to salicylic acid with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of aspirin are essentially undetectable 1.5- 3 hours after dosing.
**Distribution:** Aspirin is poorly bound to plasma proteins and its apparent volume of distribution is low (10 l). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At

low concentrations (<100 micrograms/ml), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and foetal tissues.

**Biotransformation:** The Aspirin in Clopidogrel/Aspirin is rapidly hydrolysed in plasma to salicylic acid, with a half-life of 0.3 to 0.4 hours for Aspirin doses from 75 to 100mg. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid in Clopidogrel/Aspirin has a plasma half-life of approximately 2 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20g), the plasma half-life may be increased to over 20 hours.

**Elimination:** At high aspirin doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged active substance depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acid, 10% phenolic- and 5% acylglucuronides of salicylic acid.

## 5.3. PRECLINICAL SAFETY DATA

**Clopidogrel:**

During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose. At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon. There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75mg/day). Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity. Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabeled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

**Aspirin:**

Single-dose studies have shown that the oral toxicity of Aspirin is low. Repeat-dose toxicity studies have shown that levels up to 200mg/kg/day are well tolerated in rats; dogs appear to be more sensitive, probably due to the high sensitivity of canines to the ulcerogenic effects of NSAIDs. No genotoxicity or clastogenicity issues of concern have been found with aspirin. Although no formal carcinogenicity studies have been performed with aspirin, it has been shown that it is not a tumor promoter. Reproduction toxicity data show that Aspirin is teratogenic in several laboratory animals. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. LIST OF EXCIPIENTS:

- Microcrystalline cellulose
- Pregelatinized starch
- Stearic acid
- Silicon dioxide fumed
- Hydroxypropyl methyl cellulose
- Triacetin
- Talcum powder
- Isopropyl alcohol
- Purified water
- Copolymer
- Triethyl citrate
- Eudragit
- Polysorbate
- HPC Klucel
- Mannitol
- Lactose spray dried
- Croscarmellose sodium
- Polyethylene glycol
- Tartrazine yellow lake color
- Glyceryl monostearate
- Castor oil hydrogenated
- Magnesium stearate
- Sheffcoat
- Yellow iron oxide color

### 6.2. INCOMPATIBILITIES:
Not applicable

### 6.3. SHELF LIFE:
See expiry on the pack.

### 6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

### 6.5. NATURE AND CONTENTS OF CONTAINER:
Alu/Alu blister, pack size is 10's.

### 6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### 6.7. DRUG PRODUCT SPECIFICATIONS:
SAMI's Specs.

## 7. REGISTRATION / MARKETING AUTHORISATION HOLDER
Manufactured by:
**SAMI Pharmaceuticals (Pvt.) Ltd.**
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

## 8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)
081533

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
8th August, 2016

## 10. DATE OF REVISION OF THE TEXT
N/A

# پلیٹ رڈ®-اے پی ٹیبلٹ

(کلوپیڈوگرل + اسپرین)

## ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت 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۔