PATRIOT
Pharmaceuticals Corp.

Rx

CLOPIDOGREL

Platexan®

75mg film-coated tablet
Antithrombotic

FORMULATION:
Each film-coated tablet contains:
Clopidogrel bisulfate ..... 97.875mg (equivalent to 75mg clopidogrel)

PHARMACOKINETICS:
After repeated 75 mg oral doses of clopidogrel, plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.00025 mg/L) beyond 2 hours after dosing. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivatives, and it has no effect on platelet aggregation. It represents about 85% of the circulating drug-related compounds in plasma. Following an oral dose of 14C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days. Effect of Food: Administration of clopidogrel with meals did not significantly modify the bioavailability of clopidogrel as assessed by pharmacokinetics of the main circulating metabolite. Absorption and Distribution: Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel, with peak plasma levels (=3mg/mL) of the main circulating metabolite occuring approximately 1 hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites. Clopidogrel and the main circulating metabolite bind reversibly in vitro to human plasma proteins (98% and 94%, respectively). The binding is nonsaturable in vitro up to a concentration of 100µg/ml. Metabolism and Elimination: In vitro and in vivo, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

INDICATIONS AND USAGE:
Clopidogrel is indicated for the reduction of atherothrombotic events as follows:
1. Recent MI, Recent Stroke or Established Peripheral Arterial Disease
For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, clopidogrel has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI(fatal or not), and other vascular death.
2. Acute Coronary Syndrome (ACS)
Indicated to reduce the rate of myocardial infarction and stroke (MI) in patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization. Clopidogrel should be administered in conjunction with aspirin. Indicated to reduce the rate of myocardial infarction and stroke in patients with acute ST-elevation myocardial infarction (STEMI) who are to be managed medically. Clopidogrel should be administered in conjunction with aspirin.

DOSAGE AND ADMINISTRATION:
1. Acute Coronary Syndrome
In patients who need an antiplatelet effect within hours, initiate Clopidogrel with a single 300-mg oral loading dose and then continue at 75 mg once daily. Initiating Clopidogrel without a loading dose will delay establishment of an antiplatelet effect by several days.
2. Recent MI, Recent Stroke, or Established Peripheral Arterial Disease 75 mg once daily orally without a loading dose

CONTRAINDICATIONS:
The use of clopidogrel is contraindicated in the following conditions:
1. Hypersensitivity to the drug substance or any component of the product.
2. Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS AND PRECAUTIONS:
1. Diminished Antiplatelet Activity in Patients with Impaired CYP2C19 Function
Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19.
The metabolism of clopidogrel can also be impaired by drugs that inhibit CYP2C19, such as omeprazole or esomeprazole. Avoid concomitant use of Clopidogrel bisulfate with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of Clopidogrel bisulfate.
2. General Risk of Bleeding
Thienopyridines, including Clopidogrel bisulfate, increase the risk of bleeding. Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days). Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.
3. Discontinuation of Clopidogrel bisulfate
Discontinuation of Clopidogrel bisulfate increases the risk of cardiovascular events. If Clopidogrel bisulfate must be temporarily discontinued (e.g., to treat bleeding or for surgery with a major risk of bleeding), restart it as soon as possible. When possible, interrupt therapy with Clopidogrel bisulfate for five days prior to such surgery. Resume Clopidogrel bisulfate as soon as hemostasis is achieved.
4. Thrombotic Thrombocytopenic Purpura (TTP)
TTP, sometimes fatal, has been reported following use of Clopidogrel bisulfate, sometimes after a short exposure (<2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever.
5 . Cross-Reactivity among Thienopyridines
Hypersensitivity including rash, angioedema or hematologic reaction have been reported in patients receiving Clopidogrel bisulfate, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines.

ADVERSE DRUG REACTION:
Clopidogrel has been evaluated for safety in more than 17,500 patients, including over 9,000 patients treated for 1 year or more. The overall tolerability of clopidogrel was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. The clinically important adverse events observe are discussed below.
1. Haemorrhagic disorders;
1.) In patients treated with either clopidogrel or aspirin, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was 1.4% for clopidogrel and 1.6% for aspirin. In patients that received clopidogrel,gastrointestinal hemorrhage occured at a rate 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of other bleedings was higher in patients that received clopidogrel compared to aspirin (7.3% vs. 6.5%). However, the incidence of severe events was similar in both treatment groups (0.6% vs. 0.4%). The most frequently reported events in both treatment groups were: purpura/bruising/haematoma, and epistaxis. Other less frequently reported events were haematoma, haematuria, and eye bleeding (mainly conjunctival). The incidence of intracranial bleeding was 0.4% in patients that received clopidogrel and 0.5% for patients that received aspirin.
2.)Clopidogrel use with aspirin was associated with an increase in bleeding compared to placebo with aspirin.
There was an excess in major bleeding in patients receiving clopidogrel plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fatal bleeding(0.2%), were the same in both groups. The overall incidence of bleeding is described in Table for patients receiving both clopidogrel and aspirin. Ninety-two percent (92%) of the patients study received heparin/LMWH and the rate of bleeding in these patients was similar to overall results. There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.4% clopidogrel + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel + aspirin, and 6.3% for placebo + aspirin.

Table 1. Adverse Events Occuring in ≥2.5% of Clopidogrel Patients

Body System Event	% Incidence (% Discontinuation)	
	Clopidogrel (n=9599)	Aspirin (n=9586)
Body as a Whole-general disorders		
Chest Pain	8.3(0.2)	8.3(0.3)
Accidental / Inflicted Injury	7.9(0.1)	7.3(0.1)
Influenza-like symptoms	7.5(<0.1)	7.0(<0.1)
Pain	6.4(0.1)	6.3(0.1)
Fatigue	3.3(0.1)	3.4(0.1)
Cardiovascular disorders, general		
Edema	4.1(<0.1)	4.5(<0.1)
Hypertension	4.3(<0.1)	5.1(<0.1)

Body System Event	% Incidence (% Discontinuation)	
	Clopidogrel (n=9599)	Aspirin (n=9586)
Central and peripheral nervous system disorders		
Headache	7.6(0.3)	7.2(0.2)
Dizziness	6.2(0.2)	6.7(0.3)
Gastrointestinal systems disorders		
Abdominal pain	5.6(0.7)	7.1(1.0)
Dyspepsia	5.2(0.6)	6.1(0.7)
Diarrhea	4.5(0.4)	3.4(0.3)
Nausea	3.4(0.5)	3.8(0.4)
Metabolic and nutritional disorders		
Hypercholesterolemia	4.0(0)	4.4(<0.1)
Musculo-skeletal system disorders		
Arthralgia	6.3(0.1)	6.2(0.1)
Back Pain	5.8(0.1)	5.3(<0.1)
Platelet, bleeding and clotting disorders		
Purpura/Bruise	5.3(0.3)	3.7(0.1)
Epistaxis	2.9(0.2)	2.5(0.1)
Psychiatric disorders		
Depression	3.6(0.1)	3.9(0.2)
Respiratory system disorders		
Upper resp tract infection	8.7(<0.1)	8.3(<0.1)
Dyspnea	4.5(0.1)	4.7(0.1)
Rhinitis	4.2(0.1)	4.2(<0.1)
Bronchitis	3.7(0.1)	3.7(0)
Coughing	3.1(<0.1)	2.7(<0.1)
Skin and appendage disorders		
Rash	4.2(0.5)	3.5(0.2)
Pruritis	3.3(0.3)	1.6(0.1)
Urinary system disorders		
Urinary tract infection	3.1(0)	3.5(0.1)

3. Adverse events occurring in ≥ 2.0% of patients on clopidogrel in the clinical trial are shown below regardless of relationship to clopidogrel.

Table 2. Adverse Events Occuring in ≥2.0% of Clopidogrel Patients

Body System Event	% Incidence (%Discontinuation)	
	Clopidogrel (+aspirin)* (n=6259)	Placebo (+aspirin)* (n=6303)
Body as a Whole-general disorders		
Chest Pain	2.7(<0.1)	2.8(0.0)
Central and peripheral nervous system disorders		
Headache	3.1(0.1)	3.2(0.1)
Dizziness	2.4(0.1)	2.0(<0.1)
Gastrointestinal system disorders		
Abdominal pain	2.3(0.3)	2.8(0.3)
Dyspepsia	2.0(0.1)	1.9(<0.1)
Diarrhea	2.1(0.1)	2.2(0.1)

* Other standard therapies were used as appropriate.

4. Other adverse experiences of potential importance occurring in 1 % to 2.5% of patients receiving clopidogrel in controlled clinical trials are listed below regardless of relationship to clopidogrel. In general, the incidence of these events was similar to that in patients receiving aspirin or placebo + aspirin .
- Autonomic Nervous System disorders: Syncope, Palpitation
- Body as a Whole-general disorders: Asthenia, Fever, Hernia
- Cardiovascular disorders: Cardiac failure
- Central and peripheral nervous system disorders: Cramps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertigo
- Gastrointestinal system disorders: Constipation, Vomiting
- Heart rate and rhythm disorders: Fibrillation atrial
- Liver and biliary system disorders: Hepatic enzymes increased
- Metabolic and nutritional disorders: Gout, Hyperuricemia, Non-protein nitrogen (NPN) increased
- Musculo-skeletal system disorders: Arthritis, Arthrosis
- Platelet, bleeding and clotting disorders: GI hemorrhage, hematoma, platelets decreased
- Psychiatric disorders: Anxiety, Insomia
- Red blood cell disorders: Anemia
- Respiratory system disorders: Pneumonia, Sinusitis
- Skin and appendage disorders: Eczema, Skin ulceration
- Urinary system disorders: Cystitis
- Vision disorders: Cataract, Conjunctivitis

5. Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received clopidogrel in controlled clinical trials are listed below regardless of relationship to clopidogrel.
In general, the incidence of these events was similar to that in patients receiving aspirin or placebo + aspirin .
- Body as a whole: Allergic reaction, necrosis ischemic
- Cardiovascular disorders: Edema generalized
- Gastrointestinal system disorders: Gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic
- Liver and biliary system disorders: Bilirubinemia, hepatitis infectious, liver fatty
- Platelet, bleeding and clotting disorders: Hemathrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia
- Red blood cell disorders : Anemia aplastic, anemia hypochromic
- Reproductive disorders, female: Menorrhagia
- Respiratory system disorders: Hemarthrosis
- Skin and appendage disorders: Bullous eruption, rash erythematous, rash maculopapular, urticaria
- Urinary system disorders: Abnormal renal function, acute renal failure
- White cell and reticuloendothelial system disorders: Agranulocytosis, granulocytopenia, leukemia, leucopenia, neutrophils decreased

6. Postmarketing Experience
The following events have been reported spontaneously from worldwide postmarketing experience:
"Very rare" corresponds to <1/10,000
- Blood and Lymphatic system disorders:
Very rare: Thrombotic Thrombocytopenic Purpura (TTP) (1/200,000 exposed patients), Severe Thrombocytopenia (platelet counts ≤ 30 x 10^9/ L), Granulocytopenia, Agranulocytosis, Anemia and Aplastic Anemia/Pancytopenia
- Immune system disorders:
Very rare: Anaphylactoid reactions, Serum sickness
- Psychiatric disorders:
Very rare: Confusion, Hallucinations
- Nervous system disorders:
Very rare: Taste disturbances
- Vascular disorders:
Very rare: Vasculitis, Hypotension
- Respiratory, thoracic and mediastinal disorders:
Very rare: Bronchospasm, Intestinal pneumonitis
- Gastrointestinal disorders:
Very rare: Colitis (including ulcerative and lymphocytic colitis), Pancreatitis, Stomatitis
- Hepato-biliary disorders:
Very rare: Hepatitis, Acute liver failure
- Skin and subcutaneous tissue disorders:
Very rare: Angioedema, Bullous dermatitis (erythema multiforme, Stevens Johnson Syndrome), rash erythematous, urticaria, eczema and lichen planus
- Musculoskeletal, connective tissue and bone disorders:
Very rare: Arthralgia, Arthritis, Myalgia
- Renal and urinary disorders:
Very rare: Glomerulonephritis
- General disorders and administration site conditions
Very rare: Fever
- Investigations:
Very rare: Abnormal liver function test, Blood creatinine increase

DRUG INTERACTIONS:
1. CYP2C19 Inhibitors
Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition [see Warnings and Precautions].
Omeprazole or esomeprazole
Avoid concomitant use of Clopidogrel bisulfate with omeprazole or esomeprazole. In clinical studies, omeprazole was shown to reduce significantly the antiplatelet activity of Plavix when given concomitantly or 12 hours apart. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with Plavix. Dexlansoprazole, lansoprazole and pantoprazole had less effect on the antiplatelet activity of Plavix than did omeprazole or esomeprazole [see Warnings and Precautions].
2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
Coadministration of Plavix and NSAIDs increases the risk of gastrointestinal bleeding.
3. Warfarin (CYP2C9 Substrates)
Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of Clopidogrel bisulfate with warfarin increases the risk of bleeding because of independent effects on hemostasis.
However, at high concentrations in vitro, clopidogrel inhibits CYP2C9.
4. SSRIs and SNRIs
Since selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.
5. Repaglinide (CYP2C8 Substrates)
The acyl-β-glucuronide metabolite of clopidogrel is a strong inhibitor of CYP2C8. Clopidogrel bisulfate can increase the systemic exposure to drugs that are primarily cleared by CYP2C8, thereby needing dose-adjustment and/or appropriate monitoring.

Concomitant administration of Clopidogrel bisulfate with repaglinide significantly increases systemic exposures to repaglinide. When concomitant use is required in a patient maintained on clopidogrel, initiate repaglinide at 0.5 mg with each meal and titrate based on blood glucose levels. Do not exceed a total daily dose of 4mg. If concomitant use of clopidogrel is required in a patient stabilized on higher doses of repaglinide, down titrate the dose of repaglinide based on blood glucose levels to not exceed a total daily dose of 4 mg.

USE IN SPECIFIC POPULATIONS:
1. Pregnancy
Pregnancy Category B
Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day, respectively (65 and 78 times the recommended daily human dose, respectively, on a mg/m2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, Clopidogrel bisulfate should be used during pregnancy only if clearly needed.
2. Nursing Mothers
Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from clopidogrel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
3. Pediatric Use
Safety and effectiveness in pediatric populations have not been established.
4. Geriatric Use
No dosage adjustment is necessary in elderly patients.
5. Renal Impairment
Experience is limited in patients with severe and moderate renal impairment.
6. Hepatic Impairment
No dosage adjustment is necessary in patients with hepatic impairment.

OVERDOSAGE:
Platelet inhibition by Clopidogrel bisulfate is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal hemorrhage in animals.
Based on biological plausibility, platelet transfusion may restore clotting ability.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

STORAGE:
Store at temperature not exceeding 30°C.

AVAILABILITY
Alu/Alu Blister pack x 10's (box of 30's and 100's)

Registration Number: DR-XY49142
Date of First Authorization: JULY 2024
Revision Date: AUGUST 2024

Manufactured by:
Samjin Pharm. Co., LTD.
52, Jeyakgongdan 1-gil, Hyangnam-eup,
Hwaseong-si, Gyeonggi-do, Republic of Korea

Imported and Distributed by:
Patriot Pharmaceuticals Corporation
The Patriot Building,
Km. 18 West Service Road, South Luzon Expressway,
Sucat, Parañaque City