170 mm x 105 mm

PATRIOT
Pharmaceuticals Corp.

Clopidogrel

Platexan®

75mg Tablet
Antithrombotic

FORMULATION:
Each tablet contains:
Clopidogrel (as bisulfate) 75mg

INDICATIONS:
For the prevention of atherosclerotic events in peripheral arterial disease, or within 35 days of myocardial infarction, or within 6 months of ischaemic stroke, or in acute coronary syndrome without ST-segment-elevation.

CLINICAL STUDIES
ARTHEROSCLEROTIC DISORDERS:
The use of aspirin to reduce the risk of cardiovascular events in patients with atherosclerotic vascular disorders is well established. Clopidogrel may have a role as an alternative. The CAPRIE (Ciopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) trial compared clopidogrel with aspirin in 19,815 patients at risk of ischaemic events, and found the clopidogrel reduced the risk of ischaemic stroke, myocardial infarction or death from vascular causes to a greater extent than aspirin, although the absolute difference is small.

In acute coronary symptoms. Clopidogrel may provide benefit when used in addition to aspirin. In patients with unstable angina or non- ST- elevation myocardial infarction, the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial found that the risk of cardiovascular death, myocardial infarction, or stroke was lower in patients treated with clopidogrel and aspirin, compared with those patients receiving aspirin alone. Clopidogrel was given in a loading dose of 300mg, started within 24 hours of the onset of symptoms, followed by 75mg daily for 3 to 12 months.

Similar results have been reported in patients with acute ST-elevation myocardial infarction. Clopidogrel given with aspirin and thrombolytic therapy improved the patency of the affected artery and reduced the incidence of ischaemic complications at 30 days, while a further study found that the addition of clopidogrel to aspirin and standard therapy (including thrombolytics in over half of the patients) also reduced early mortality.

Use of clopidogrel with aspirin has also been studied in ischaemic stroke but any benefit appears to be outweighed by an increased risk of bleeding. In the MATCH (Aspirin and Clopidogrel compared with clopidogrel alone alter recent ischaemic stroke or transient ischaemic attack, in high risk patients) study, adding aspirin to clopidogrel did not reduce the incidence of vascular events compared with clopidogrel alone, but the risk of major or life threatening bleeding was increased.

REPERFUSION AND REVASCULARISATION PROCEDURES:
Percutaneous coronary intervention (PI) has an established role in the management of both acute and stable coronary disease. Coronary stents are widely used during PCI to treat and prevent restenosis, but thrombotic occlusion may complicate their use. Antiplatelet drugs are therefore used to reduce this risk. A regimen of long-term aspirin with ticlopidine for 4 weeks has been widely used, However, use of ticlopidine is associated with haematological toxicity and clopidogrel has been studied as an alternative. Observational studies indicated the clopidogrel and ticlopidine produced similar benefits. In a subsequent randomized trial CLASSICS (Clopidogrel Aspirin Stent International Cooperative Study), in which clopidogrel was given in a dose of 75 mg daily for 28 days, with or without a 300mg-loading dose, the combination of clopidogrel with aspirin appeared to be as effective as ticlopidine with aspirin and was also better tolerated. Clopidogrel with aspirin is therefore recommended for patients undergoing stenting. The optimum dose of clopidogrel is unclear; a loading does of 300mg should be given at least 6 hours before the procedure, but there is some evidence that a dose of 600mg may be preferable if the procedure is carried out sooner. However, there has been some concern that use of a loading dose may cause bleeding complications if patients are found to be unsuitable for PCI and require urgent coronary artery bypass grafting.

Following the procedure, clopidogrel should be continued in a dose of 75mg daily with aspirin, for at least 2 weeks (or longer if a drug-eluting stent is used); continuation for up to 12 months may provide additional benefit, and at least 9 to 12 months treatment is generally advised. In the PCI-CURE study, long term treatment with clopidogrel and aspirin also reduced the risk of major cardiovascular events following PCI , with or without stenting, for unstable angina.

CONTRAINDICATION
Hypersensitivity to the active substance or to any of the excipients, severe hepatic impairment and active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

ADVERSE EFFECTS:
The incidence of adverse effecls, particularly dyscrasias, is lower with clopidogrel, although fatalities have been reported . Other adverse effects, reported rarely, include serum sickness, interstitial pneumonitis, etrythema multiforme, Stevens-Johnson syndrome, lichen planus, and myalgia. Consideration should be given to stopping clopidogrel 5 to 7 days before elective surgery.

Pregnancy and Lactation
There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, It is preferable not to use clopidogrel during pregnancy as a precautionary measure.

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel film-coated tablet.

INTERACTIONS:
Clopidogrel should be used with caution in patients receiving other drugs that increase the risk of bleeding, including anticoagulants, other antiplatelets, and NSAIDs. Clopidogrel may inhibit the cytochrome P450 isoenzyme CYP2C9 and interactions with drugs metabolized by this isoenzyme are theoretically possible; it may also inhibit CYP2B6.

A study of healthy individuals found that clopidogrel reduced the conversion of bupropion to its active metabolite, suggesting that clopidogrel inhibits the cytochrome P450 isoenzyme CYP2B6.

Myopathy and rhabdomyolusis may occur in patients receiving ciclosporin with a statin. However, there are case reports of patients stabilized without incident on ciclosporin and a stalin (atorvastatin, lovastatin or simvastatin) who developed rhabdomyolysis about 1 to 3 weeks after clopidogrel was added on the treatment.

EFFECT OF FOOD:
Administration of clopidogrel with meals did not significantly modify the bioavailability of clopidogrel.

"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph"

PHARMACODYNAMICS
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.

PHARMACOKINETICS:
Clopidogrel is rapidly but incompletely absorbed after oral doses; absorption appears to be at least 56%. It is a prodrug and is extensively metabolized in the liver, mainly to the inactive carboxylic acid derivative. The active metabolite appears to be a thiol derivative but has not been identified in plasma. Clopidogrel and the carboxylic acid derivative are highly protein bound. Clopidogrel and its metabolites are excreted in urine and in faeces; about 50% of an oral dose is recovered from the urine and about 46% from the faeces.

DOSAGE AND ADMINISTRATION:
Prophylaxis of thromboembolic events - 75mg once daily

Management of acute coronary syndromes including unstable angina and non-Q wave myocardial infarction – clopidogrel is given as a single 300mg loading dose, followed by 75mg daily. Or as prescribed by the physician.

Clopidogrel is given by mouth as the bisulfate, but doses are expressed in terms of the base: 97.86 mg of clopidogrel bisulfate is equivalent to 75mg of base

OVERDOSAGE
Platelet inhibition is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal hemorrhage in animals. Appropriate therapy should be considered if bleedings are observed.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY: Box of 30 tablets (10 tablets per blister)
: Box of 15 tablets (15 tablets per blister)

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STORE AT TEMPERATURES NOT EXCEEDING 30°C.

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