CLOPIDOGREL

ZEROCLOT

75 mg Film-Coated Tablet
ANTITHROMBOTIC
(PLATELET AGGREGATION INHIBITORS)

Rx

FORMULATION:
Each film-coated tablet contains:
Clopidogrel (as Bisulfate) USP ....75 mg

PRODUCT DESCRIPTION:
A reddish brown colored, round, biconvex, film-coated tablet.

PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin.

Mechanism of action:
Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.
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.

Pharmacodynamic effects:
Repeated doses of 75 mg 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 75 mg 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.

PHARMACOKINETICS:
Clopidogrel is rapidly but incompletely absorbed after oral doses; absorption appears to be at least 50%. It is a prodrug and is extensively metabolized in the liver, mainly to the inactive carboxylic acid derivative. The active metabolite appears to be a thiol derivative but has been identified in plasma. Clopidogrel and the carboxylic acid derivative are highly protein bound. Clopidogrel and its metabolites are excreted in urine and in feces; about 50% of an oral dose is recovered from the urine and about 46% from feces.

INDICATIONS:
For the reduction of atherosclerotic events (myocardial infarction, stroke or vascular death) in patients with atherosclerosis documented by recent stroke, myocardial infarction, or established peripheral arterial disease. For treatment of patients suffering from non-ST sequel elevation, acute coronary syndrome (unstable angina or non-Q wave myocardial infarction) including patients undergoing stent placement following percutaneous coronary intervention or combination with ASA in medically treated patients eligible from thrombolytic therapy.

DOSAGE AND ADMINISTRATION:
Acute coronary syndrome: Loading dose of 300 mg followed by 75 mg daily.
Prophylaxis of thromboembolic events: The usual dose is 75 mg once daily.
Management of acute coronary syndromes, unstable angina and non-Q wave myocardial infaction: 300 mg loading dose, followed by 75 mg once daily.

CONTRAINDICATIONS:
Clopidogrel is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients in the formulations. Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Bleeding and hematological disorders
Due to the risk of bleeding and hematological 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 ASA, Heparin, Glycoprotein IIb/IIIa inhibitors or Non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), 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 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. Patients should inform physicians and dentists that they are taking Clopidogrel before any surgery is scheduled and before any new medicinal product is taken. 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 ASA), and that they should report any unusual bleeding (site or duration) to their physician.

Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of Clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic hemolytic anemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

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

Recent ischemic stroke
In view of the lack of data, Clopidogrel cannot be recommended during the first 7 days after acute ischemic stroke.

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 metabolized 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 hematological cross-reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or hematological 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
Clopidogrel contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. This medicinal product contains hydrogenated castor oil which may cause stomach upset and diarrhea.

FERTILITY, PREGNANCY AND LACTATION:
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.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Breast-feeding:
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, breastfeeding should not be continued during treatment with Clopidogrel.

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

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

ADVERSE EFFECTS:
Gastrointestinal disturbances, skin rashes, blood dyscrasias including neutropenia and thrombocytopenic purpura, hemorrhagic disorders, hepatitis and cholestatic jaundice.

DRUG INTERACTIONS:
Aspirin: Potentiates the effect of aspirin on collagen-induced platelet aggregation.
NSAID: Risk of increased occult gastrointestinal blood loss.
Phenytoin, Tamoxifen, Tolbutamide, Warfarin, Torsemide, fluvastatin; since Clopidogrel inhibits CYP4502C9, it may interfere with the metabolism of these drugs.

OVERDOSAGE AND TREATMENT:
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.

WARNING:
Thrombotic thrombocytopenic purpura sometimes after a short exposure (less than 2 weeks).

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

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30ºC.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

AVAILABILITY:
Alu/Alu Blister pack of 10's (box of 100's)

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