For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory only.

DEPLATT

(Clopidogrel Tablets U.S.P.)

COMPOSITION

Each film coated tablet contains :
Clopidogrel Bisulfate equivalent to
Clopidogrel.....75 mg
Colours : Red oxide of Iron and Titanium dioxide
Excipients.....q.s

PRODUCT DESCRIPTION

Light Pink coloured, round, bevelled edge, biconvex film coated tablets plain on both sides.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS:

Mechanism of Action

Clopidogrel is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established cardiovascular atherosclerotic disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, unstable angina or the need for vascular bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate.

Pharmacodynamic Properties

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel. Repeated doses of 75 mg clopidogrel per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg clopidogrel per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

PHARMACOKINETICS

After repeated 75-mg oral doses of clopidogrel (base), 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 derivative, and it too has no effect on platelet aggregation. It represents about 85% of the circulating drug-related compounds in plasma.

Following an oral dose of ^{14}C-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 the pharmacokinetics of the main circulating metabolite.

Absorption and Distribution: Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels (≅3 mg/L) of the main circulating metabolite occurring 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 100 µg/mL.

Metabolism and Elimination:

Clopidogrel is extensively metabolized by the liver. In vitro and *in vivo*, clopidogrel is metabolized 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. Cytochromes first oxidize clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. The oxidative step is regulated primarily by Cytochrome P450 ISOENZYMES 2B6, 3A4, 1A1, 1A2 and 2C19. Subsequent metabolism of the 2oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel.

Special Populations

Geriatric Patients: Plasma concentrations of the main circulating metabolite are significantly higher in elderly (≥75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

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Renally Impaired Patients: After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of clopidogrel per day.

Gender: No significant difference was observed in the plasma levels of the main circulating metabolite between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study, the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Race: Pharmacokinetic differences due to race have not been studied.

INDICATIONS AND USAGE

Clopidogrel is indicated to prevent atherothrombotic events in adults as given below.

- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.
- Patients suffering from acute coronary syndrome:
  - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Qwave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention.
  - ST segment elevation acute myocardial infarction, in combination with acetylsalicyclic acid (ASA) in medically treated patients eligible for thrombolytic therapy.

CONTRAINDICATIONS

The use of clopidogrel is contraindicated in the following conditions:

- Hypersensitivity to the drug substance or any component of the product.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.
- Severe liver impairment
- Breast-feeding.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

WARNINGS

Thrombotic thrombocytopenic purpura (TTP): TTP has been reported rarely following use of clopidogrel, sometimes after a short exposure (<2 weeks). TTP is a serious condition requiring prompt treatment. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. TTP was not seen during clopidogrel's clinical trials, which included over 17,500 clopidogrel-treated patients. In world-wide postmarketing experience, however, TTP has been reported at a rate of about four cases per million patients exposed, or about 11 cases per million patient-years. The background rate is thought to be about four cases per million person-years.

PRECAUTIONS

Pharmacogenetics: Based on literature data, patients with genetically reduced CYP22C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function.

General

As with other antiplatelet agents, clopidogrel prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, clopidogrel should be discontinued 5 days prior to surgery.

Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment.

GI Bleeding: In clinical trials clopidogrel was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin and the incidence of major gastrointestinal bleeding was 1.3% vs 0.7% (clopidogrel + aspirin vs placebo + aspirin, respectively.) clopidogrel should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking clopidogrel.

Use in Hepatically Impaired Patients: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Clopidogrel should be used with caution in this population.

Use in Renally Impaired Patients: Experience is limited in patients with severe renal impairment. Clopidogrel should be used with caution in this population.

Information for Patients

Patients should be told that it may take them longer than usual to stop bleeding when they take clopidogrel, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Since clopidogrel is metabolized to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g proton pump inhibitors) should be discouraged.

Study of specific drug interactions yielded the following results:

Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by clopidogrel. Clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregation. Clopidogrel and aspirin have been administered together for up to one year.

Heparin: In a study in healthy volunteers, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by clopidogrel.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of clopidogrel was associated with increased occult gastrointestinal blood loss. NSAIDs and clopidogrel should be coadministered with caution.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken with caution.

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when clopidogrel was coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of clopidogrel was also not significantly influenced by the coadministration of phenobarbital, cimetidine or estrogen.

The pharmacokinetics of digoxin or theophylline was not modified by the coadministration of clopidogrel.

At high concentrations *in vitro*, clopidogrel inhibits P_{450} (2C9). Accordingly, clopidogrel may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with clopidogrel.

In addition to the above specific interaction studies, patients entered into clinical trials with clopidogrel received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, hormone replacement therapy, heparins (unfractionated and LMWH) and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions. The use of oral anticoagulants, non-study anti-platelet drug and chronic NSAIDs was not allowed in clinical trials and there are no data on their concomitant use with clopidogrel.

Drug/laboratory test interactions-Not known.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg.

Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice). Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m^2 basis).

PREGNANCY

PREGNANCY CATEGORY B. Reproduction studies performed in rats and rabbits, revealed that no evidence of impaired fertility or fetotoxicity due to clopidogrel. However, there are no adequate and well-controlled studies in pregnant women because animal reproduction studies are not always predictive of a human response, clopidogrel should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Clopidogrel has been evaluated for safety in many patients. The overall tolerability of clopidogrel in clinical trials was similar to that of aspirin.

Most frequent adverse events reported with clopidogrel in the clinical trials are shown below regardless of relationship to clopidogrel.

Body as a Whole - general disorders
Chest Pain, Accidental/Inflicted Injury, Influenza-like symptoms, Pain, Fatigue
Cardiovascular disorders, general
Oedema, Hypertension
Central & peripheral nervous system disorders
Headache, Dizziness
Gastrointestinal system disorders
Abdominal pain, Dyspepsia, Diarrhoea, Nausea
Metabolic & nutritional disorders
Hypercholesterolemia
Musculo-skeletal system disorders
Arthralgia, Back Pain
Platelet, bleeding, & clotting disorders
Purpura/Bruise, Epistaxis
Psychiatric disorders
Depression
Respiratory system disorders
Upper respiratory tract infection, Dyspnea, Rhinitis, Bronchitis, Coughing
Skin & appendage disorders
Rash, Pruritus
Urinary system disorders
Urinary tract infection

Other reported adverse experiences of potential importance occurring in patients receiving clopidogrel are listed below regardless of relationship to clopidogrel.

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 & clotting disorders: GI haemorrhage, hematoma, platelets decreased.
Psychiatric disorders: Anxiety, Insomnia.
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.

OVER DOSAGE

In a reported over dosage of a single 1,050mg dose of clopidogrel (equivalent to 14 standard 75mg tablets); there were no associated adverse events. No special therapy was instituted, and she recovered without sequelae.

No adverse events were reported after single oral administration of 600 mg (equivalent to 8 standard 75mg tablets) of clopidogrel in healthy volunteers.

Symptoms of acute toxicity includes vomiting (in baboons), prostration, difficult breathing, and gastrointestinal haemorrhage in all species.

Recommendations about Specific Treatment

Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of clopidogrel if quick reversal is required.

DOSAGE AND ADMINISTRATION

Adults and elderly

Clopidogrel should be given as a single dose of 75 mg/day with or without food.

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 300-mg loading dose and then continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75mg-325mg daily). The dose of ASA should not be higher than 100 mg since ASA at higher doses is associated with high bleeding risk. The optimal duration of treatment has not been formally established. Literatures support use up to 12 months, and the maximum benefit was seen at 3 months.

ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a 300-mg loading dose in combination with ASA and with or without thrombolytics. For patients over 75 years of age Clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied.

Paediatric patients

The safety and efficacy of clopidogrel in children and adolescents have not yet been established.

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.

Mode of administration: Oral

STORAGE

Store below 30^{o}C, Protected from light & moisture.

PRESENTATION

Deplatt tablets is packed in Alu-Alu blisters of 10 tablets Such blisters containing 10 tablets are packed into boxes of 30's and 100's.

"Not all presentations may be available locally"

EXPIRY DATE

24 months from the date of Manufacturing.

Date of Revision

April, 2010

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TORRENT PHARMACEUTICALS LTD.
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