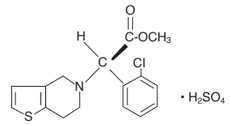
For the use of a registered Medical Practitioner or a Hospital or a Laboratory. xxxxxxxx-8883

DEPLATT

(Clopidogrel Tablets U.S.P., 75 mg)

COMPOSITION :
Each film coated tablet contains Clopidogrel Bisulfate U.S.P. equivalent to Clopidogrel 75 mg.
DESCRIPTION :
DEPLATT is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of subsequent ADP-mediated activation of the glycoprotein GP IIb/IIIa complex. Chemically, it is methyl (+)-(S)_α-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c] pyridine-5 (4H)-acetate sulfate (1:1).



CLINICAL PHARMACOLOGY :
Mechanism of Action
After activation by cytochrome P450 (CYP)-mediated hepatic metabolism, DEPLATT selectively and irreversibly inhibits ADP-induced platelet aggregation. At a clinically relevant dosage (75 mg/day), DEPLATT prevented ADP-induced inhibition of adenylate cyclase and binding of fibrinogen without modifying the glycoprotein (GP) IIb/IIIa complex in platelets obtained from healthy volunteers. The drug also abolished cyclic AMP-dependent phosphorylation of vasodilator-simulated phosphoprotein, an event associated with activation of the GP IIb/IIIa complex.
Pharmacokinetics
DEPLATT is rapidly converted to an inactive carboxylic acid metabolite (SR 26334) after absorption from the gastrointestinal tract. Administrations of DEPLATT with food and antacids doesnot significantly alter the bioavailability. Plasma concentrations of SR 26334 increase linearly in proportion to the dose after single dose of administration of 50-150 mg DEPLATT. DEPLATT and SR 26334 are irreversibly and avidly (98 and 94% respectively) bound in a nonsaturable manner to human plasma proteins in vitro. DEPLATT and its metabolite do not distribute in the red blood cells to a substantial extent. The elimination half-life of SR 26334 is about 7-8 hours after both single and multiple dose administration. Approximately 50 and 46% of radiolabelled DEPLATT is eliminated in the urine and faeces, respectively, within 5 days of oral administration.
INDICATIONS :
DEPLATT is indicated for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease.
CONTRAINDICATIONS :
The use of DEPLATT 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 hemorrhage.
WARNINGS :
Patients should be told that it might take them longer than usual to stop bleeding when they take DEPLATT, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking DEPLATT before any surgery is scheduled and before any new drug is taken.
PRECAUTIONS :
General
As with other antiplatelet agents, DEPLATT should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions or drug therapy. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, DEPLATT should be discontinued 7 days prior to surgery.
GI Bleeding
DEPLATT prolongs the bleeding time. In CAPRIE, DEPLATT was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. DEPLATT should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions (such as aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]) should be used with caution in patients taking DEPLATT.
Use in Hepatic Impaired Patients
Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. DEPLATT should be used with caution in this population.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY :
There was no evidence of tumorigenicity when DEPLATT 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.
DEPLATT was not genotoxic in four *in vitro* tests and in one *in vivo* test.
DEPLATT 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 CATEGORY B :
DEPLATT should be used during pregnancy only if clearly needed.
Nursing Mothers
Animal studies do not show that DEPLATT 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, 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.
DRUG INTERACTIONS :
Aspirin
Aspirin did not modify the DEPLATT-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 DEPLATT. DEPLATT potentiated the effect of aspirin on collagen-induced platelet aggregation. The safety of chronic concomitant administration of aspirin and DEPLATT has not been established.
Heparin
DEPLATT did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on inhibition of platelet aggregation induced by DEPLATT. The safety of this combination has not been established, however, and concomitant use should be undertaken with caution.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
Concomitant administration of DEPLATT was associated with increased occult gastrointestinal blood loss in healthy volunteers receiving naproxen. NSAIDs and DEPLATT should be co-administered with caution.
Warfarin
The safety of the co-administration of DEPLATT with warfarin has not been established. Consequently, concomitant administration of these two agents should be undertaken with caution.
Other Concomitant Therapy
No clinically significant pharmacodynamic interactions were observed when DEPLATT was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of DEPLATT was also not significantly influenced by the co-administration of phenobarbital, cimetidine or estrogen.
The pharmacokinetics of digoxin or theophylline was not modified by the co-administration of DEPLATT).
At high concentrations in vitro, DEPLATT inhibits P450 (2C9). Accordingly, DEPLATT 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 DEPLATT.
In addition to the above specific interaction studies, patients entered into CAPRIE received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents, antiepileptic agents and hormone replacement therapy without evidence of clinically significant adverse interactions.
OVERDOSAGE :
One case of deliberate overdosage with DEPLATT was reported in the large, controlled clinical study. A 34-year-old woman took a single 1,050-mg dose of DEPLATT (equivalent to 14 standard 75-mg 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 75-mg tablets) of DEPLATT in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75 mg of DEPLATT per day.
A single oral dose of DEPLATT at 1500 or 2000 mg/kg was lethal to mice, to rats, and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.
ADVERSE EFFECTS :
In CAPRIE, the most common clinically important side effects with DEPLATT were pruritus, purpura, diarrhoea and rash; infrequent events included intracranial hemorrhage (0.4%) and severe neutropenia (0.04%).
The worldwide post marketing experience with DEPLATT reported thrombotic thrombocytopenic purpura (TTP) at the rate of 4 cases per million patients.
DOSAGE AND ADMINISTRATION :
DEPLATT is administered orally. The recommended dose is 75 mg once daily with or without food. No dosage adjustment is necessary for elderly patients or patients with renal disease.
Pediatric Use
Safety and effectiveness in the pediatric population have not been established.
EXPIRY DATE :
Do not use later than the date of expiry.
STORAGE :
Store below 30°C, protected from light and moisture
PRESENTATION AND AVAILABILITY :
Deplatt is available as light pink coloured, round, biconvex, film coated tablets, in strip of 10 tablets & Blister strip of 10 & 2 tablets.

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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