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

TORPLATT

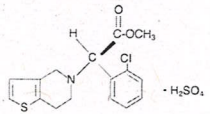
(Clopidogrel Bisulfate Tablets U.S.P.)

COMPOSITION

Each film coated tablet of TORPLATT contains Clopidogrel Bisulfate U.S.P equivalent to Clopidogrel.....75 mg.

DESCRIPTION

TORPLATT 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, TORPLATT selectively and irreversibly inhibits ADP-induced platelet aggregation. At a clinically relevant dosage (75 mg/day), TORPLATT 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

TORPLATT is rapidly converted to an inactive carboxylic acid metabolite (SR 26334) after absorption from the gastrointestinal tract. Administrations of TORPLATT 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 TORPLATT. TORPLATT and SR 26334 are irreversibly and avidly (98 and 94% respectively) bound in a nonsaturable manner to human plasma proteins in vitro. TORPLATT 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 TORPLATT is eliminated in the urine and faeces, respectively, within 5 days of oral administration.

INDICATIONS

TORPLATT 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 TORPLATT 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 TORPLATT, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking TORPLATT before any surgery is scheduled and before any new drug is taken.

Drug interactions: Co-administration of TORPLATT with omeprazole, a proton pump inhibitor that is an inhibitor of CYP2C19, reduces the pharmacological activity of TORPLATT if given concomitantly or if given 12 hours apart. There is no evidence that other drugs that reduce stomach acid, such as most H2 blockers (except cimetidine, which is a CYP2C19 inhibitor) or antacids interfere with the antiplatelet activity of clopidogrel. (see **PRECAUTIONS: Drug Interactions**).

PRECAUTIONS

General

As with other antiplatelet agents, TORPLATT 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, TORPLATT should be discontinued 7 days prior to surgery.

GI Bleeding

TORPLATT prolongs the bleeding time. In CAPRIE, TORPLATT was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. TORPLATT 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 TORPLATT.

Use in Hepatic Impaired Patients

Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. TORPLATT should be used with caution in this population.

DRUG INTERACTIONS

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. Avoid concomitant use of drugs that inhibit CYP2C19, including omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine (see WARNINGS).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

There was no evidence of tumorigenicity when TORPLATT 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.

TORPLATT was not genotoxic in four *in vitro* tests and in one *in vivo* test.

TORPLATT 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

TORPLATT should be used during pregnancy only if clearly needed.

Nursing Mothers

Animal studies do not show that TORPLATT 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 TORPLATT-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 TORPLATT. TORPLATT potentiated the effect of aspirin on collagen-induced platelet aggregation. The safety of chronic concomitant administration of aspirin and TORPLATT has not been established.

Heparin

TORPLATT 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 TORPLATT. 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 TORPLATT was associated with increased occult gastrointestinal blood loss in healthy volunteers receiving naproxen, NSAIDs and TORPLATT should be co-administered with caution.

Warfarin

The safety of the co-administration of TORPLATT 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 TORPLATT was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of TORPLATT 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 with TORPLATT.

At high concentrations *in vitro*, TORPLATT inhibits P_{450} (2C9). Accordingly, TORPLATT 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 TORPLATT.

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 Clopidogrel was reported in the large, controlled clinical study. A 34-year-old woman took a single 1,050 mg dose of Clopidogrel (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 500 mg (equivalent to 8 standard 75 mg tablets) of Clopidogrel 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 Clopidogrel per day.

A single oral dose of Clopidogrel 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 TORPLATT were pruritus, purpura, diarrhoea and rash; infrequent events included intracranial hemorrhage (0.4%) and severe neutropenia (0.04%).

The worldwide post marketing experience with TORPLATT reported thrombotic thrombocytopenic purpura (TTP) at the rate of 4 cases per million patients.

DOSAGE AND ADMINISTRATION

TORPLATT 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

TORPLATT is available light pink coloured, round, biconvex, film coated tablets in strip of 10 tablets.

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Baddi 173 205, Dist. Solan (H.P.) INDIA.