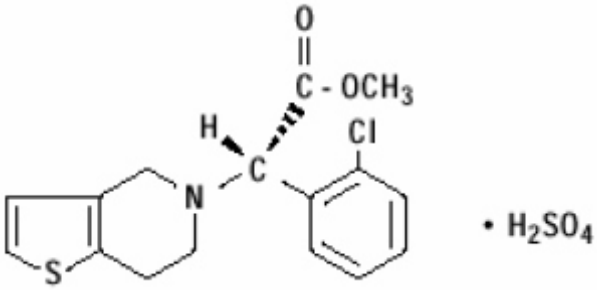
Taj Pharmaceuticals Ltd.

Clopidogrel Bisulfate

CAS No. : 135046-48-9

DRUG DESCRIPTION

(clopidogrel bisulfate) is a thienopyridine class inhibitor of P2Y 12 ADP platelet receptors. Chemically it is methyl (+)- (S)-a-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5 (4H)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is C16H16ClNO2S•H2SO4 and its molecular weight is 419.9.



Clopidogrel bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

Plavix for oral administration is provided as either pink, round, biconvex, debossed, film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base or pink, oblong, debossed film-coated tablets containing 391.5 mg of clopidogrel bisulfate which is the molar equivalent of 300 mg of clopidogrel base.

Each tablet contains hydrogenated castor oil, hydroxypropylcellulose, mannitol, microcrystalline cellulose and polyethylene glycol 6000 as inactive ingredients. The pink film coating contains ferric oxide, hypromellose 2910, lactose monohydrate, titanium dioxide and triacetin. The tablets are polished with Carnauba wax.

INDICATIONS

Acute Coronary Syndrome (ACS)

For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization, Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

For patients with ST-elevation myocardial infarction (STEMI), Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary percutaneous coronary intervention is unknown.

The optimal duration of Plavix therapy in ACS is unknown. Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Plavix has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

WARNINGS

Thrombotic thrombocytopenic purpura (TTP)

TTP has been reported rarely following use of clopidogrel bisulfate, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. (See ADVERSE REACTIONS.)

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TAJ PHARMACEUTICALS LIMITED.
Working For Healthier World™ INDIA

PRECAUTIONS

General
Clopidogrel bisulfate 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 bisulfate 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 (see ADVERSE REACTIONS).
In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and clopidogrel bisulfate has not been shown to be more effective than clopidogrel bisulfate alone, but the combination has been shown to increase major bleeding.

GI Bleeding
In CAPRIE, clopidogrel bisulfate was associated with a rate of gastrointestinal bleeding of 2%, vs. 2.7% on aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs 0.7% (clopidogrel bisulfate + aspirin vs. placebo + aspirin, respectively). Clopidogrel bisulfate 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 bisulfate.

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

Use in Renally Impaired Patients
Experience is limited in patients with severe renal impairment. Clopidogrel bisulfate 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, that they may bruise and/or bleed more easily when they take clopidogrel bisulfate or clopidogrel bisulfate combined with aspirin, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking clopidogrel bisulfate and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.

Pregnancy
Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel bisulfate should be used during pregnancy only if clearly needed.

Nursing Mothers
Studies in rats have shown that clopidogrel 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.

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

Geriatric Use
Of the total number of subjects in controlled clinical studies, approximately 50% of patients treated with clopidogrel bisulfate were 65 years of age and over. Approximately 16% of patients treated with clopidogrel bisulfate were 75 years of age and over.

The observed difference in risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Figure 3 (see CLINICAL STUDIES). The observed difference in risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Table 3 (see ADVERSE REACTIONS).

DOSAGE AND ADMINISTRATION
Recent MI, Recent Stroke or Established Peripheral Arterial Disease
The recommended daily dose of clopidogrel tablets is 75 mg once daily.

Acute Coronary Syndrome
For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), clopidogrel bisulfate should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with clopidogrel bisulfate. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely (see CLINICAL STUDIES).

Clopidogrel tablets can be administered with or without food.
No dosage adjustment is necessary for elderly patients or patients with renal disease (See Clinical Pharmacology: Special Populations.)

SIDE EFFECTS

The tolerability of clopidogrel is similar to that of aspirin. Diarrhea, rash, or itching occurs in approximately 1 in 20 persons taking clopidogrel. Abdominal pain also occurs in about 1 in 20 persons, but it is less frequent than with aspirin.

Ticlopidine (Ticlid) is an antiplatelet medication quite similar to clopidogrel. It has been associated with a severe reduction in white blood cell count in between 0.8% and 1% of persons. The risk of this dangerous side effect with clopidogrel is about 0.04%, much less than with ticlopidine but twice that of aspirin

Clopidogrel rarely causes a condition called thrombotic thrombocytopenic purpura (TTP) in one out of every 250,000 people. TTP is a serious condition in which blood clots form throughout the body. Blood platelets, which participate in clotting, are consumed, and the result can be bleeding because enough platelets are no longer left to allow blood to clot normally. For comparison, the related drug, ticlodipine (Ticlid), causes TTP 17-50 times more frequently than clopidogrel.

CNS: depression, dizziness, fatigue, headache

CV: chest pain, hypertension

EENT: epistaxis, rhinitis

GI: diarrhea, abdominal pain, dyspepsia, gastritis, GI bleeding

Hematologic: bleeding, neutropenia, thrombotic thrombocytopenic purpura

Metabolic: hypercholesterolemia, gout

Musculoskeletal: joint pain, back pain

Respiratory: cough, dyspnea, bronchitis, upper respiratory tract infection, bronchospasm

Skin: pruritus, rash, angioedema

Other: hypersensitivity reactions, anaphylactic reactions

INTERACTION

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significanceAspirin orNonsteroidal anti-inflammatory drugs (NSAIDs) (concurrent use of clopidogrel with these agents may increase the risk of gastrointestinal bleedingaspirin has not been found to modify the clopidogrel-mediated inhibiton of ADP-induced platelet aggregation, nor has it been found to increase the prolongation of bleeding time induced by clopidogrel; however, clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregationFluvastatin or Nonsteroidal anti-inflammatory drugs (NSAIDs) or
Phenytoin or
Tamoxifen or
Tolbutamide or
Torsemide or
Warfarin (because clopidogrel inhibits hepatic cytochrome P450 enzyme activity at high concentrations in vitro , a possibility exists that it could interfere with the metabolism of these medications; caution is recommendedHeparin or Warfarin (safety of concurrent use has not been established; caution is recommended

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