CILOSTAZOL

CILOSTAN CR

200 mg Controlled-Release Tablet
Platelet Aggregation Inhibitor

Rx

FORMULATION
Each Controlled-Release Tablet contains:
Cilostazol ..... 200 mg

DESCRIPTION
White, oblong, controlled release tablet, engraved with "UT" on one side and "C200" on the other side

PHARMACODYNAMICS
Mechanism of Action
The mechanism of the effects of Cilostazol on the symptoms of intermittent claudication is not fully understood. Cilostazol and several of its metabolites are cyclic AMP (cAMP) phosphodiesterase III inhibitors (PDE III inhibitors), inhibiting phosphodiesterase activity and suppressing cAMP degradation with a resultant increase in cAMP in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation, respectively.

Cardiovascular Effects
Cilostazol affects both vascular beds and cardiovascular function. It produces non-homogeneous dilation of vascular beds, with greater dilation in femoral beds than in vertebral, carotid or superior mesenteric arteries. Renal arteries were not responsive to the effects of Cilostazol.
In dogs or cynomolgous monkeys, Cilostazol increased heart rate, myocardial contractile force, and coronary blood flow as well as ventricular automaticity, as would be expected for a PDE III inhibitor. Left ventricular contractility was increased at doses required to inhibit platelet aggregation. A-V conduction was accelerated. In humans, heart rate increased in a dose-proportional manner by a mean of 5.1 and 7.4 beats per minute in patients treated with 50 and 100 mg b.i.d., respectively. In 264 patients evaluated with Holter monitors, numerically more Cilostazol-treated patients had increases in ventricular premature beats and non-sustained ventricular tachycardia events than did placebo-treated patients; the increases were not dose-related.

PHARMACOKINETICS
Absorption
Cilostazol is absorbed after oral administration. A high fat meal increases absorption, with an approximately 90% increase in C_{max} and a 25% increase in AUC. Absolute bioavailability is not known. Cilostazol is extensively metabolized by hepatic cytochrome P-450 enzymes, mainly 3A4, and, to a lesser extent, 2C19, with metabolites largely excreted in urine. Two metabolites are active, with one metabolite appearing to account for at least 50% of the pharmacologic (PDE III inhibition) activity after administration of Cilostazol. Pharmacokinetics is approximately dose proportional. Cilostazol and its active metabolites have apparent elimination half-lives of about 11 to 13 hours. Cilostazol and its active metabolites accumulate about 2-fold with chronic administration and reach steady state blood levels within a few days. The pharmacokinetics of Cilostazol and its two major active metabolites were similar in healthy normal subjects and patients with intermittent claudication due to peripheral arterial disease (PAD).

Distribution
Plasma Protein and Erythrocyte Binding:
Cilostazol is 95 - 98% protein bound, predominantly to albumin. The mean percent binding for 3,4-dehydro-cilostazol is 97.4% and for 4′-trans-hydroxy-cilostazol is 66%. Mild hepatic impairment did not affect protein binding. The free fraction of cilostazol was 27% higher in subjects with renal impairment than in normal volunteers. The displacement of cilostazol from plasma proteins by erythromycin, quinidine, warfarin, and omeprazole was not clinically significant.

Metabolism and Excretion:
Cilostazol is eliminated predominately by metabolism and subsequent urinary excretion of metabolites. Based on in vitro studies, the primary isoenzymes involved in cilostazol's metabolism are CYP3A4 and, to a lesser extent, CYP2C19. The enzyme responsible for metabolism of 3,4-dehydro-cilostazol, the most active of the metabolites, is unknown.
Following oral administration of 100 mg radiolabeled cilostazol, 56% of the total analytes in plasma was cilostazol, 15% was 3,4-dehydro-cilostazol (4-7 times as active as cilostazol), and 4% was 4′-trans-hydroxy-cilostazol (one fifth as active as cilostazol). The primary route of elimination was via the urine (74%), with the remainder excreted in feces (20%). No measurable amount of unchanged cilostazol was excreted in the urine, and less than 2% of the dose was excreted as 3,4-dehydro-cilostazol. About 30% of the dose was excreted in urine as 4′-trans-hydroxy-cilostazol. The remainder was excreted as other metabolites, none of which exceeded 5%. There was no evidence of induction of hepatic microenzymes.

Special Populations:
Age and Gender:
The total and unbound oral clearances, adjusted for body weight, of cilostazol and its metabolites were not significantly different with respect to age and/or gender across a 50-to-80-year-old age range.

Smokers:
Population pharmacokinetic analysis suggests that smoking decreased cilostazol exposure by about 20%.

Hepatic Impairment:
The pharmacokinetics of cilostazol and its metabolites were similar in subjects with mild hepatic disease as compared to healthy subjects.
Patients with moderate or severe hepatic impairment have not been studied.

Renal Impairment:
The total pharmacologic activity of cilostazol and its metabolites was similar in subjects with mild to moderate renal impairment and in normal subjects. Severe renal impairment increases metabolite levels and alters protein binding of the parent and metabolites. The expected pharmacologic activity, however, based on plasma concentrations and relative PDE III inhibiting potency of parent drug and metabolites, appeared little changed. Patients on dialysis have not been studied, but it is unlikely that cilostazol can be removed efficiently by dialysis because of its high protein binding (95 - 98%).

INDICATIONS
Cilostazol (Cilostan CR) is used in the treatment of ischemic symptoms including ulcer, pain and coldness of the extremities in chronic arterial occlusion. It is also indicated in the prevention of reoccurence of cerebral infarction (excluding cardiogenic cerebral embolism).

DOSAGE & ADMINISTRATION
The recommended dose is 200 mg daily, taken as one dose (every 24 hours).
It should be taken at least 30 minutes before or 2 hours after food.

CONTRAINDICATIONS
Patients with any known predisposition to bleeding (e.g., active peptic ulceration, recent (within six months) haemorrhagic stroke, proliferative diabetic retinopathy, poorly controlled hypertension).
Patients with a congestive heart failure.
Patients who have shown hypersensitivity to this product or any of its components.
Pregnant women or women of childbearing potential.

PRECAUTIONS
Patients who are using anticoagulant such as warfarin; platelet aggregation inhibitor including aspirin, ticlopidine, etc.; and thrombolytic including urokinase and alteplase since it may cause bleeding.
Patients who are using prostaglandin E1 or derivative (alprostadile, rimaprodex, alphadex, etc) since bleeding may also occur.
Patients with menstruation.
Severe renal impairment: creatinine clearance of ≤25 mL/min.
Moderate or severe hepatic impairment.
Patients with any known predisposition to bleeding (e.g., active peptic ulceration, recent (within six months) haemorrhagic stroke, proliferative diabetic retinopathy, poorly controlled hypertension).
Patients with any history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics, whether or not adequately treated, and in patients with prolongation of the QTc interval.

ADVERSE EFFECTS
Serious adverse effects
Encephalorrhagia, pneumorrhagia, fundus bleeding, occasionally, suffusion, or rarely enteral bleeding, nasal hemorrhage, hematuria may occur. If they occur, the administration should be discontinued and appropriate treatment must be done.
Pancytopenia, agranulocytosis, rarely thrombocytopenia may occur. If they occur, the administration should be discontinued and appropriate treatment must be done.
Interstitial pneumonia, accompanied with flush, cough, dyspnea, disorder of chest, eosinophilia may occur. If these symptoms occur, the administration should be discontinued and appropriate treatment must be done including adenocortical hormone therapy.
Congestive heart failure, cardiac infarction, angina pectoris, ventricular tachycardia, etc. have been reported. If they occur, the administration should be discontinued and/or appropriate therapy instituted.
Occasionally, elevations of AST, ALT, ALP, LDH and icterus may occur, patients should be observed sufficiently. If any symptoms occur, the administration should be discontinued or reduced.
Others

Hypersensitivity: Occasionally, eruption, or rarely, epidermatomycosis, urticaria, itch, photosensitivity reaction may occur. If they occur, the administration should be discontinued.
Cardiovascular: Arrhythmia such as arterial fibrillation, ventricular tachycardia, premature ventricular contraction, decline in blood pressure, occasionally, frequent pulse, ardor, and rarely, blood pressure increase may occur. If they occur, dose reduction or discontinuation can be considered.
CNS: Tremors, occasional headache, dizziness, or rarely, insomnia, and drowsiness may occur. If they occur, dose reduction or discontinuation can be considered.
Gastrointestinal: Abdominal pain, nausea, vomiting, anorexia, and diarrhea may occur occasionally, or brash, abdominal inflation may occur rarely.
Kidney: Increases of BUN, creatinine, and uratic value may occur rarely.
Hemic and Lymphatic: Anemia, ecchymosis, iron deficiency anemia, polycythemia, purpura.
Metabolic and Nutritional: Increased creatinine, gout, hyperlipemia, hyperuricemia.
Musculoskeletal: Arthralgia, bone pain, bursitis.
Nervous: Anxiety, insomnia, neuralgia.
Endocrine: Diabetes mellitus
Respiratory: Asthma, epistaxis, hemoptysis, pneumonia, sinusitis.
Skin and Appendages: Dry skin, furunculosis, skin hypertrophy, urticaria
Special Senses: Amblyopia, blindness, conjunctivitis, diplopia, ear pain, eye haemorrhage, retinal haemorrhage, tinnitus.
Urogenital: Albuminuria, cystitis, urinary frequency, vaginal haemorrhage, vaginitis.
Other: Pyrexia, occasionally, sweating, edema or rarely, increment blood sugar, chest pain, tinnitus, dolorific, malaise, conjunctivitis, urinary frequency may occur.

GENERAL PRECAUTIONS
Cilostazol (Cilostan CR) may cause dizziness and patients should be warned to exercise caution before they drive or operate machinery.
Taking cilostazol with food has been shown to increase the maximum plasma concentrations (C_{max}) of cilostazol, which may be associated with an increased incidence of adverse effects.
Cilostazol is an inhibitor of PDE III. It has been reported that in long term administration, comparative experiment of congestive heart failure patient (NYHA class III-IV), survival rate of cardiotonic inhibiting PDE III is lower than placebo as for cardiotonic inhibiting PDE III.
Patients should be warned to report any episode of bleeding or easy bruising whilst on therapy. In case of retinal bleeding, administration of cilostazol should be stopped.
In addition to reporting episodes of bleeding and easy bruising, patients should be warned to promptly report any other signs which might also suggest the early development of blood dyscrasia such as pyrexia and sore throat. A full blood count should be performed if infection is suspected or there is any other clinical evidence of blood dyscrasia. Cilostazol should be discontinued promptly if there is clinical or laboratory evidence of haematological abnormalities.

DRUG INTERACTIONS
Cilostazol is extensively metabolized by CYP enzymes, particularly CYP3A4 and CYP2C19.
Concomitant administration with anticoagulant drugs such as warfarin; platelet aggregation inhibitors like aspirin, ticlopidine etc.; and thrombolytics including urokinase and alteplase may cause bleeding.
Concomitant intake with prostaglandin E1 or derivative (alprostadile, rimaprodex, alphadex, etc) may also cause bleeding.
In patients receiving Cilostazol and inhibitors of CYP3A4 (erythromycin, cimetidine, grape fruit juice) concomitantly, increase in blood levels of these drugs may be observed. In these cases, the administration should be reduced or started at lower dosage.
In patients receiving Cilostazol and organic of CYP3A4 (diltiazem) concomitantly, increase in blood levels of these drugs may be observed. If used concomitantly, the administration should be reduced or started at lower dosage.
In patients receiving Cilostazol and inhibitors of CYP3A4 (omeprazole, etc.) concomitantly, blood levels of these drugs may be increased. If used concomitantly, the administration should be reduced or started at lower dosage.

USE IN PREGNANCY AND LACTATION
In animal (rat) studies, low birth weight infant and death have been reported therefore, Cilostazol should not be used in pregnant women or women of childbearing potential.
Transfer of Cilostazol into milk has been reported in experimental animals (rats). Because of the potential risk to nursing infants, a decision should be made to discontinue nursing or to discontinue Cilostazol intake.

USE IN THE ELDERLY
Particular care should be taken in the elderly since usually their physiologic function may be lowered.

USE IN CHILDREN
Safety and efficacy in children have not been established.

OVERDOSE
Information on acute overdose with Cilostazol in humans is limited. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: severe headache, diarrhea, hypotension, tachycardia, and possibly cardiac arrhythmias. The patient should be carefully observed and given supportive treatment. Since cilostazol is highly protein-bound, it is unlikely that it can be efficiently removed by hemodialysis or peritoneal dialysis. The oral LD50 of cilostazol is >5.0 g/kg in mice and rats and >2.0 g/kg in dogs.

OTHERS
In subjects with severe renal impairment, the free fraction of Cilostazol was 27% higher and both C_{max} and AUC were 29% and 39% lower respectively than in subjects with normal renal function. The C_{max} and AUC of the dehydro metabolite were 41% and 47% lower respectively in the severely renally impaired subjects compared to subjects with normal renal function. The C_{max} and AUC of 4'-trans-hydroxy cilostazol were 173% and 209% greater in subjects with severe renal impairment. The drug should not be administered to patients with a creatinine clearance <25 mL/min.
In repeated oral administration study with beagle for 13 weeks and 52 weeks, hypertrophic endocardium and coronary arteriography disorder occurred in high dosage. Non- toxic dose is 30 mg/kg/day, 12 mg/kg/day. This change was observed only in dogs and not in rat and monkey. And inhibition of PDE III and vasodilation have occurred in same situation.

STORAGE
Store at temperatures not exceeding 30°C.

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

AVAILABILITY
In Alu / Clear PVC Blister Pack x 10's (Box of 3 blister packs x 10 tablets)

Keep out of reach of children.

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.

Date of first authorization / approval – 16 February 2016
Date of revision – 07 November 2022

KOREA UNITED PHARM. INC.
25-23, Nojanggongdan-gil, Jeondong-myeon, Sejong-si, Korea

Manufactured by
KOREA UNITED PHARM. INC.
25-23, Nojanggongdan-gil, Jeodong-Myeon,
Sejong-si, Korea

Imported & Distributed by the Marketing Authorization Holder (MAH)

ONE PHARMA

ONE PHARMA MARKETING INC.
L51 B21 Abel Nosce St., BF Resort Village,
Talon II, Las Piñas City, Metro Manila

3410202363-21027PHL