Cilostazol

Trombocil®
50 mg and 100 mg Tablet
antiplatelet / peripheral vasodilator

FORMULATION

Each tablet contains:
Cilostazol ..……..……..……..……...50 mg or 100 mg

PRODUCT DESCRIPTION

50 mg Tablet: White, round, biconvex tablet, 1/4“ in diameter, plain on both sides
100 mg Tablet: White, round, biconvex tablet, 5/16” in diameter, plain on both sides

CLINICAL PHARMACOLOGY

Pharmacodynamics

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.

Cilostazol affects both vascular beds and cardiovascular function. It produces non-homogenous dilation of vascular beds, with greater dilation in femoral beds than in vertebral, carotid, or superior mesenteric arteries. Renal arteries are not responsive to the effects of cilostazol.

Effects on circulating plasma lipids have been examined in patients taking cilostazol. After 12 weeks, cilostazol 100 mg twice daily produced a reduction in triglycerides of 29.3 mg/dL (15%) and an increase in HDL-cholesterol of 4 mg/dL (~10%) compared to placebo.

Pharmacokinetics

Cilostazol is absorbed after oral administration. A high-fat meal increases absorption, with about 90% increase in peak plasma concentration (C_{max}) and 25% increase in area under the time-concentration curve (AUC). Absolute bioavailability is unknown.

Cilostazol is extensively metabolized by hepatic cytochrome P-450 enzymes, mainly 3A4, to a lesser extent, 2C19, and to an even lesser extent, CYP1A2, with metabolites largely excreted in urine. There are two major metabolites, 3,4-dehydro-cilostazol and 4’-trans-hydroxy-cilostazol. The dehydro metabolite is 4 to 7 times as active a platelet antiaggregant as the parent compound and the 4’-trans-hydroxy metabolite is one fifth as active. Plasma concentrations (measured by AUC) of the dehydro and 4’-trans-hydroxy metabolites are ~41% and ~12% of cilostazol concentrations.

Cilostazol and its active metabolites have apparent elimination half-lives of about 11 to 13 hours. Cilostazol and its active metabolites accumulate about two-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).

Cilostazol is 95 to 98% protein bound, predominantly to albumin. The mean percent binding for 3,4-dehydro-cilostazol and 4’-trans-hydroxy-cilostazol are 97.4% and 66%, respectively.

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%. No evidence of induction of hepatic microenzymes was observed.

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 in the 50 to 80 year old range.

Smokers
Smoking decreased cilostazol exposure by about 20% in population pharmacokinetic analysis.

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 cilostazol and its metabolites. The expected pharmacologic activity, however, based on plasma concentrations and relative PDE III inhibiting potency of cilostazol and its metabolites, appeared little changed.

Bioequivalence Study
Cilostazol (Trombocil®) 100 mg tablet was shown to be bioequivalent to the reference product (innovator) in adults under fasting conditions. The following are important pharmacokinetic parameters of cilostazol in adult volunteers who received cilostazol (Trombocil®) 100 mg tablet (as a single oral dose) under fasting conditions:

Pharmacokinetic Parameters	Cilostazol 100 mg Tablet	90% Confidence Interval
Tmax (hour)	3.27 ± 1.22	–
Cmax ± S.D. (mcg/mL)	1.07 ± 0.18	94.601 – 108.464
$AUC_{0\text{-}48h}$ ± S.D. (mcg-h/mL)	18.04 ± 4.91	94.770 – 109.838
$AUC_{0\text{-}inf}$ ± S.D. (mcg-h/mL)	19.51 ± 4.88	86.354 – 102.634
Kel (hour)	0.08 ± 0.04	–
$T_{1/2}$ (hour)	11.01 ± 7.37	–

T max = time the drug reached its maximum concentration in the blood
C max = maximum plasma concentration of the drug at peak time
$AUC_{0\text{-}48h}$ = area under the curve from blood level profile (from zero to sampling time point)
$AUC_{0\text{-}inf}$ = area under the curve from blood level profile (extrapolated to infinity)
Kel = elimination rate constant
$T_{1/2}$ = elimination half-life

INDICATIONS
- Treatment of ischemic symptoms including ulceration, pain, and coldness of the extremities in chronic arterial occlusion
- Prevention of recurrence of cerebral infarction (excluding cardiogenic cerebral embolism)

DOSAGE AND ADMINISTRATION
General Dosing Recommendations:
- Individualize dosage according to patient's clinical response.

- Taking cilostazol with food increases the maximum cilostazol plasma concentrations, which may be associated with increased incidence of adverse effects.
- Patients may respond as early as 2 to 4 weeks after the initiation of therapy, but treatment for up to 12 weeks may be needed before a beneficial effect is experienced.

Recommended Oral Adult Dose: 100 mg twice daily, taken at least half an hour before or two hours after breakfast and dinner.

Coadministration with Cytochrome Inhibitors* (see **INTERACTIONS WITH OTHER MEDICAMENTS):** 50 mg twice daily
*CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin diltiazem)
*CYP2C19 inhibitors (e.g., omeprazole)

Discontinuation of Therapy: Available data suggest that cilostazol dosage can be reduced or discontinued without rebound platelet hyperaggregability.

CONTRAINDICATIONS
Cilostazol is contraindicated in:
- Patients with congestive heart failure of any severity. Cilostazol and several of its metabolites are phosphodiesterase III inhibitors. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III to IV congestive heart failure.
- Patients with known or suspected hypersensitivity to any of its components
- Patients with any known predisposition to bleeding such as active peptic ulceration, hemorrhagic stroke within the last six months, proliferative diabetic retinopathy, poorly controlled hypertension
- Patients with any history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics, whether or not adequately treated
- Patients with prolongation of the QT_c interval
- Patients with history of severe tachyarrhythmia
- Patients with unstable angina pectoris, myocardial infarction/coronary intervention within the last six months
- Patients treated concomitantly with two or more additional antiplatelet or anticoagulant agents (e.g., aspirin, clopidogrel, heparin, warfarin, acenocoumarol, dabigatran, rivaroxaban or apixaban)
- Pregnancy

WARNINGS AND PRECAUTIONS

WARNING: DECREASED SURVIVAL IN HEART FAILURE PATIENTS

Cilostazol is contraindicated in patients with congestive heart failure of any severity. Cilostazol and several of its metabolites are phosphodiesterase III inhibitors. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III to IV congestive heart failure.

Cardiovascular Effects: Cilostazol may induce tachycardia, palpitation, tachyarrhythmia and/or hypotension. The increase in heart rate associated with cilostazol is approximately 5 to 7 bpm. Patients with a history of ischemic heart disease may be at risk for exacerbations of angina pectoris or myocardial infarction.

Left ventricular outflow tract obstruction has been reported in patients with sigmoid shaped interventricular septum. Monitor patients for the development of a new systolic murmur or cardiac symptoms after initiating cilostazol.

Hematologic Adverse Reactions: There have been case reports of thrombocytopenia or leukopenia progressing to agranulocytosis when cilostazol was not immediately discontinued. Agranulocytosis was reversible on discontinuation of cilostazol. Periodically monitor platelet and white blood cell counts.

Cilostazol inhibits platelet aggregation in a reversible manner. Cilostazol has not been studied in patients with hemostatic disorders or active pathologic bleeding. Avoid use of cilostazol in these patients.

Patients should report any episode of bleeding or easy bruising during therapy. Discontinue cilostazol in cases of retinal bleeding.

The risk of intraocular bleeding may be higher in patients with diabetes.

Patients should 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. Immediately discontinue cilostazol if there is clinical or laboratory evidence of hematologic abnormalities.

Use in Surgery: Because of cilostazol's platelet aggregation inhibitory effect, it is possible that an increased bleeding risk occurs in combination with surgery (including minor invasive procedures like tooth extraction). If a patient is to undergo elective surgery and antiplatelet effect is not necessary, discontinue cilostazol five days before surgery.

Hepatic Impairment: Patients with moderate or severe hepatic impairment have not been studied in clinical trials. Special caution is advised when cilostazol is administered in such patients.

Renal Impairment: 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 to 98%). Special caution should be exercised when cilostazol is used in patients with severe renal impairment (creatinine clearance <25 mL/min).

Effects on Ability to Drive and Use Machines
Cilostazol may cause dizziness. Patients should exercise caution when driving vehicles or operating machinery.

INTERACTIONS WITH OTHER MEDICAMENTS
Aspirin: Coadministration increased inhibition of ADP-induced *ex vivo* platelet aggregation when compared to aspirin alone.
Clopidogrel and other antiplatelet agents: Coadministration of clopidogrel did not have any effect on platelet count, prothrombin time, or activated partial thromboplastin time. Multiple doses of clopidogrel did not significantly increase steady state cilostazol plasma concentrations. Caution is advised when cilostazol is coadministered with any drug that inhibits platelet aggregation. Monitor the bleeding time at intervals. Cilostazol is contraindicated in patients receiving two or more additional antiplatelet/anticoagulant agents.
Warfarin and other anticoagulant agents: Cilostazol does not inhibit either the metabolism or pharmacologic effects (prothrombin time, activated partial thromboplastin time, bleeding time, platelet aggregation) of R- and S-warfarin after a single 25-mg dose of warfarin. Caution is advised in patients receiving both cilostazol and any anticoagulant agent. Frequent monitoring is required to reduce the possibility of bleeding. Cilostazol is contraindicated in patients receiving two or more additional antiplatelet/anticoagulant agents.
Strong inhibitors of CYP3A4: A priming dose of ketoconazole 400 mg was given one day prior to coadministration of single doses of ketoconazole 400 mg and cilostazol 100 mg. This regimen increased cilostazol C_{max} by 94% and AUC by 117%. Other strong inhibitors of CYP3A4 (e.g., itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline) would be expected to have a similar effect.

Moderate inhibitors of CYP3A4:

- ***Erythromycin and other macrolide antibiotics:*** Coadministration of erythromycin 500 mg every 8 hours with a single dose of cilostazol 100 mg increased cilostazol C_{max} by 47% and AUC by 73%. Inhibition of cilostazol metabolism by erythromycin increased the AUC of 4′-trans-hydroxy-cilostazol by 141%. Other macrolide antibiotics would be expected to have similar effect.
- ***Diltiazem:*** Decreased cilostazol clearance by about 30%; cilostazol C_{max} and AUC increased by about 30% and 40%, respectively.
- ***Grapefruit juice:*** Increased cilostazol C_{max} by about 50% but had no effect on AUC.

Inhibitors of CYP2C19:

- ***Omeprazole:*** Coadministration of omeprazole did not significantly affect cilostazol metabolism, but the systemic exposure to 3,4-dehydro-cilostazol was increased by 69%, probably the result of omeprazole's potent inhibition of CYP2C19.
- ***Quinidine:*** Did not alter cilostazol pharmacokinetics
- ***Lovastatin:*** Decreased cilostazol $C_{ss,max}$ and AUC by 15% and cilostazol metabolite concentrations (although nonsignificant); increased lovastatin and beta-hydroxy-lovastatin AUC by about 70%.

Inducers of CYP3A4 and CYP2C19 (e.g., carbamazepine, phenytoin, rifampicin, St. John's wort): The antiplatelet effect may be altered and should be carefully monitored.

STATEMENT ON USAGE FOR HIGH-RISK GROUPS

Pregnancy: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Cilostazol should not be used during pregnancy.

Lactation: 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 breastfeeding or to discontinue cilostazol.

Elderly: Pharmacokinetic studies have not shown any age-related effects on the absorption, distribution, metabolism, and elimination of cilostazol and its metabolites.

Children: The safety and effectiveness of cilostazol in pediatric patients have not been established.

UNDESIRABLE EFFECTS

The most frequently reported adverse effects with cilostazol include headache, diarrhea, abnormal stools, and palpitations.

Infections and infestations: Infection
Blood and lymphatic system disorders: Agranulocytosis, anemia, aplastic anemia, bleeding tendency, bleeding time prolonged, ecchymosis, granulocytopenia, leukopenia, pancytopenia, thrombocythemia, thrombocytopenia, increased eosinophils
Immune system disorders: Allergic reaction, anaphylaxis, angioedema
Metabolism and nutrition disorders: Anorexia, diabetes mellitus, edema (peripheral, face), hyperglycemia, hyperuricemia
Psychiatric disorders: Anxiety
Nervous system disorders: Abnormal dreams, cerebral hemorrhage, cerebrovascular accident, dizziness, dull headache, hypoesthesia, insomnia, intracranial hemorrhage, paresis, sleepiness, tremor, vertigo
Eye disorders: Conjunctivitis, eye hemorrhage, retinal hemorrhage
Ear and labyrinth disorders: Tinnitus
Cardiac disorders: Angina pectoris, arrhythmia, atrial fibrillation, congestive heart failure, myocardial infarction, nodal arrhythmia, supraventricular extrasystoles, supraventricular tachycardia, syncope, tachycardia, *Torsades de pointes* and QTc prolongation in patients with cardiac disorders (e.g., complete atrioventricular block, heart failure, and bradyarrhythmia), ventricular extrasystoles, ventricular tachycardia

Vascular disorders: Epistaxis, hemorrhage (unspecified), hot flushes, hypertension, hypotension, orthostatic hypotension, subacute stent thrombosis
Respiratory, thoracic and mediastinal disorders: Cough, dyspnea, interstitial pneumonia, pharyngitis, pneumonia, pulmonary hemorrhage, respiratory tract hemorrhage, rhinitis
Gastrointestinal disorders: Abdominal distention, abdominal pain, diarrhea, dysguesia, dyspepsia, flatulence, gastritis, gastrointestinal hemorrhage, heartburn, melena, nausea, vomiting
Hepatobiliary disorders: Hepatic dysfunction/abnormal liver function tests, hepatitis, jaundice, increases in: alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH)
Skin and subcutaneous tissue disorders: Alopecia, eczema, photosensitivity, pruritus, rash, skin drug eruption (dermatitis medicamentosa), skin eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, subcutaneous hemorrhage
Musculoskeletal and connective tissue disorders: Muscle hemorrhage, myalgia
Renal and urinary disorders: Hematuria, pollakiuria, renal failure, renal impairment
General disorders and administration site conditions: Asthenia, chest pain, chills, generalized edema, malaise, pain, pyrexia, sweating, weakness
Investigations: Increases in blood creatinine, blood glucose, blood pressure, blood urea nitrogen, uric acid level; decrease in blood pressure
Injury, poisoning and procedural complications: Extradural hematoma, subdural hematoma

OVERDOSE AND TREATMENT
Information on acute overdosage with cilostazol in humans is limited. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect (e.g., severe headache, diarrhea, hypotension, tachycardia, possibly cardiac arrhythmias).

Carefully observe patient and give supportive treatment. The stomach should be emptied by induced vomiting or gastric lavage, as appropriate. Since cilostazol is highly protein-bound, it is unlikely that it can be efficiently removed by hemodialysis or peritoneal dialysis.

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

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph.
By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Cilostazol (Trombocil®) 50 mg Tablet, in flex foil x 10s (box of 100s)
Cilostazol (Trombocil®) 100 mg Tablet, in flex foil x 10s (box of 100s)

STORE AT TEMPERATURES NOT EXCEEDING 30°C
KEEP THE PRODUCT OUT OF SIGHT AND REACH OF CHILDREN

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