CILOSTAZOL
VAXOL

100 mg Tablet

PLATELET AGGREGATION INHIBITOR

FORMULATION
Each uncoated tablet contains:
Cilostazol ..... 100 mg

PRODUCT DESCRIPTION
White,smooth, round, flat faced bevelled edge, uncoated tablets with break line on one side and plain on the other side.

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.

Pharmacokinetics
Absorption
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.
Metabolism
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.
Distribution
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).
Elimination
Cilostazol and its active metabolites have apparent elimination half-lives of about 11 to 13 hours.
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-hydroxyCilostazol. The remainder was excreted as other metabolites, none of which exceeded 5%. No evidence of induction of hepatic microenzymes was observed.

INDICATIONS
It is used in the management of peripheral vascular disease.

DOSAGE AND ADMINISTRATION
The recommended dosage of Cilostazol is 100 mg orally twice daily taken at least half an hour before or two hours after breakfast or dinner.

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.

Discontinuation of Therapy: The available data suggest that the dosage of Cilostazol can be reduced or discontinued without rebound (i.e., platelet hyperaggregability).

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

DRUG INTERACTIONS
Aspirin: Co-administration increased inhibition of ADP-induced ex vivo platelet aggregation when compared to aspirin alone.
Clopidogrel and other antiplatelet agents: Co-administration 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 co-administration of single doses of ketoconazole 400 mg and Cilostazol 100 mg. This regimen increased Cilostazol Cmax by 94% and AUC by 117%. Other strong inhibitors of CYP3A4 (e.g., itraconazole, fluconazole, miconazol, fluvoxamine, fluoxetine, nefazodone, sertraline) would be expected to have a similar effect.
Moderate inhibitors of CYP3A4:
• **Erythromycin and other macrolide antibiotics:** Co-administration of erythromycin 500 mg every 8 hours with a single dose of Cilostazol 100 mg increased Cilostazol Cmax 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 Cmax and AUC increased by about 30% and 40%, respectively.
• **Grapefruit juice:** Increased Cilostazol Cmax by about 50% but had no effect on AUC.
Inhibitors of CYP2C19:
• **Omeprazole:** Co-administration 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 Css,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.

ADVERSE DRUG REACTIONS
The only adverse event resulting in discontinuation of therapy in >3 % of patients treated with Cilostazol 50 or 100 mg b.i.d, was headache, which occurred with an incidence of 1.3%, 3.5%, and 0.3% in patients treated with Cilostazol 50 mg b.i.d., 100 mg b.i.d., or placebo respectively. Other frequent causes of discontinuation included palpitation and diarrhea, both 1.1% for Cilostazol (all doses) versus 0.1% for placebo.

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: severe headache, diarrhea, hypotension, tachycardia, and possibly cardiac arrhythmias. Patients should be observed and given supportive treatment. The stomach should be emptied by induced vomiting or gastric lavage, as appropriate.

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.

PREGNANCY
Pregnancy Category C
In a rat developmental toxicity study, oral administration of 1000 mg Cilostazol/kg/day was associated with decreased fetal weights and increased incidences of cardiovascular, renal, and skeletal anomalies (ventricular septal, aortic arch, and subclavian artery abnormalities; renal pelvic dilation; 14th rib; and retarded ossification).

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.

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.

Use with clopidogrel
There is no information with respect to the efficacy or safety of the concurrent use of Cilostazol and clopidogrel, a platelet aggregation inhibiting drug indicated for use in patients with peripheral arterial disease. Studies of concomitant use of Cilostazol and clopidogrel are planned.

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

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.

STORAGE CONDITION
Store at temperatures not exceeding 25ºC.

Keep all medicines out of reach of children.

AVAILABILITY
Blister Pack x 10's (Box of 100's)

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