

PLETAAL[®]

Tablets 50 & 100

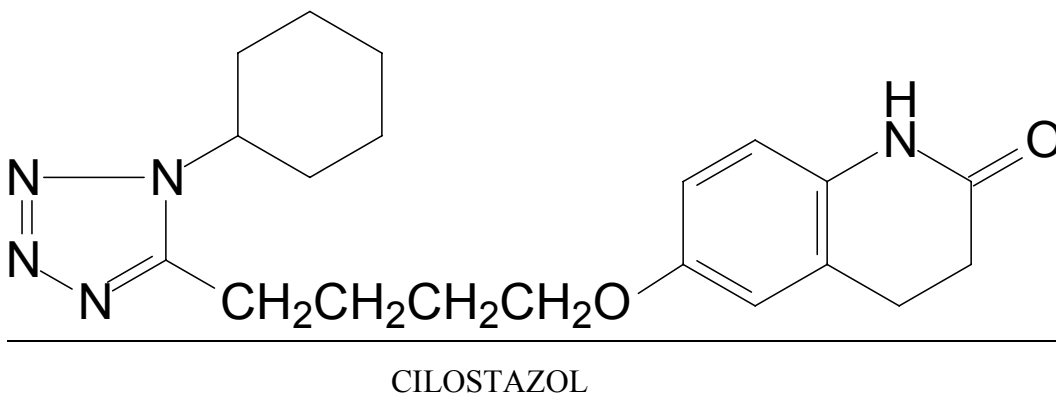
(PLA-tal)

(*cilostazol*) (sil-OS-tah-zol)

Tablets

DESCRIPTION

PLETAAL (*cilostazol*) is a quinolinone derivative that selectively inhibits phosphodiesterase III (cGMP-inhibited phosphodiesterase). The empirical formula of *cilostazol* is C₂₀H₂₇N₅O₂, and its molecular weight is 369.47. *Cilostazol* is 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl) butoxy]-3,4-dihydro-2(1*H*)-quinolinone. The structural formula is:



Cilostazol occurs as white to off-white crystals or as a crystalline powder that is slightly soluble in methanol and ethanol, and is practically insoluble in water, 0.1 N HCl, and 0.1 N NaOH.

COMPOSITION

Each PLETAAL 50 tablet contains 50 mg of *cilostazol*.

Each PLETAAL 100 tablet contains 100 mg of *cilostazol*.

INDICATIONS

Treatment of ischemic symptoms including ulceration, pain, and coldness of the extremities in chronic arterial occlusion and for the reduction of symptoms of intermittent claudication, as indicated by an increased walking distance.

Prevention of recurrence of cerebral infarction (excluding cardiogenic cerebral embolism)

Precautions

The effects of PLETAAL on cerebral infarction have not been studied in patients with asymptomatic cerebral infarction.

DOSAGE AND ADMINISTRATION

The usual adult dose of PLETAAL Tablets is 100 mg of *cilostazol*, twice daily, by the oral route taken at least half an hour before or two hours after breakfast and dinner. The dosage may be adjusted according to the age of the patient and the severity of symptoms.

Precautions concerning use

Patients should be instructed to remove the tablets from the press-through package (PTP) before taking the medication. (Swallowing of the PTP has led to serious complications such as esophageal perforation and mediastinitis).

Discontinuation of Therapy

The available data suggest that the dosage of PLETAAL can be reduced or discontinued without rebound (i.e. platelet hyperaggregability).

CONTRAINDICATIONS

PLETAAL is contraindicated in the following patients:

- ❖ Patients with hemorrhage (e.g., hemophilia, increased capillary fragility, intracranial hemorrhage, hemorrhage in the digestive tract, hemorrhage in the urinary tract, hemoptysis, and hemorrhage in the vitreous body. (Bleeding tendency may be increased).
- ❖ Patients with congestive heart failure. (Condition may be worsened). (See under Important Precautions). *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. PLETAAL (*cilostazol*) is contraindicated in patients with congestive heart failure of any severity.
- ❖ Patients with a history of hypersensitivity to any ingredient of the drug.
- ❖ Women who are pregnant or may possibly become pregnant (See Use during Pregnancy, Delivery, or Lactation.)

WARNINGS

Patients should be closely monitored for any anginal symptoms (e.g., chest pain), since treatment with PLETAAL may increase pulse rate, which could induce angina pectoris. [A significant increase in PRP (pressure rate product) was observed during long-term administration of PLETAAL in a clinical study to evaluate the drug's efficacy in the prevention of cerebral infarction.] (See under Important Precautions, Clinically Significant Adverse Reactions and Clinical Studies).

PRECAUTIONS

Careful Administration

This drug should be administered with caution in the following patients:

- i. Patients on anticoagulants (e.g., warfarin), antiplatelet drugs (e.g. aspirin, ticlopidine), thrombolytic drugs (e.g., urokinase and alteplase), or prostaglandin E₁, or its derivatives (e.g., alprostadil and limaprost alfadex). (See Drug Interactions).
- ii. Patients with a bleeding tendency or a predisposition to bleeding (If bleeding occurs, bleeding tendency may be increased.)
- iii. Patients with coronary artery stenosis. (Increased pulse rate possibly resulting from treatment with PLETAAL could induce angina pectoris).(See under Important Precautions, under Clinically significant adverse reactions and under Clinical Studies).
- iv. Patients with diabetes mellitus or abnormal glucose tolerance. (Hemorrhagic adverse events may occur).
- v. Patients with severe hepatic impairment. (The blood concentration of *cilostazol* may be increased.) (See Pharmacokinetics)
- vi. Patients with severe renal impairment. (The blood concentration of *cilostazol* and its metabolites may be increased). (See Pharmacokinetics)
- vii. Patients during menstruation. (There is a risk of menorrhagia.)
- viii. Patients of severe hypertension with consistently high blood pressure (e.g., malignant hypertension). (See under Other Precautions).

Important Precautions

PLETAAL should not be administered to patients with cerebral infarction until their condition has stabilized.

If an excessive increase in pulse rate is observed in patients with coronary artery stenosis during treatment with PLETAAL, the dosage should be reduced or the drug discontinued and appropriate corrective measures taken, since the increased pulse rate could induce angina pectoris. (See under Careful Administration, clinically significant adverse reactions and under Clinical Studies).

PLETAAL is a drug with PDE3 inhibitory activity. Long-term comparative studies of cardiostonic agents with PDE3 inhibitory activity (milrinone and vesnarinone) in patients with congestive heart failure (NYHA class III to IV) demonstrated lower survival rates in patients receiving such cardiostonic agents compared with patients receiving placebo. In addition, prognosis following long-term treatment with PDE3 inhibitors, including PLETAAL, has not yet been determined in patients without congestive heart failure.

Other Precautions

Endocardial thickening and coronary arterial lesions were observed at high doses in 13- and 52-week oral repeated-dose toxicity studies of *cilostazol* in beagle dogs. The non-toxic doses were 30 and 12 mg/kg/day respectively. These cardiac changes were not observed in either rats or monkeys. In 1-week intravenous repeated-dose cardiotoxicity studies, changes in the left ventricular endocardium, right atrial epicardium, and coronary arteries were observed in dogs and mild hemorrhagic changes in the left ventricular endocardium were observed in monkeys. Cardiac changes have also been reported in studies of other PDE inhibitors and vasodilators, and dogs are considered to be highly sensitive in showing such changes.

The mean survival time of stroke-prone spontaneously hypertensive rats (SHR-SP) given 0.3% cilostazol in the diet was shorter than that of control animals (40.2 weeks versus 43.5 weeks).

In a clinical study to evaluate PLETAAL's efficacy in the prevention of recurrence of cerebral infarction, diabetes mellitus occurred or was worsened in more patients in the PLETAAL group (11/520 patients) than in the placebo group (1/523 patients).

Coadministration of a single dose of lovastatin 80 mg with a single dose of PLETAAL 100 mg increased lovastatin AUC by 64% compared with administration of lovastatin alone.

Use In Pregnancy, Delivery or Lactation

PLETAAL should not be used in women who are pregnant or who may possibly become pregnant. In a rat development toxicity study, oral administration of 1000mg *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). At this dose, systemic exposure to unbound *cilostazol* in nonpregnant rats was about 5 times the exposure in humans given the maximum recommended human dose (MRHD). Increased incidences of ventricular septal defect and retarded ossification were also noted at 150 mg/kg/day (5 times the MRHD on systemic exposure basis). In a rabbit developmental toxicity study, an increased incidence of retardation of ossification of the sternum was seen at doses as low as 150 mg/kg/day. In nonpregnant rabbits given 150 mg/kg/day, exposure to unbound *cilostazol* was considerably lower than that seen in humans given the MRHD, and exposure to 3,4-dehydro-cilostazol was barely detectable.

When *cilostazol* was administered to rats during late pregnancy and lactation, an increased incidence of stillborn and decreased birth weights of offspring was seen at doses of 150 mg/kg/day (5 times the MRHD on a systemic exposure basis). There are no adequate and well-controlled studies in pregnant women.

Nursing should be suspended during use of the drug by nursing women. (Rat studies showed that PLETAAL was distributed to breast milk in nursing rats).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dietary administration of *cilostazol* to male and female rats and mice for up to 104 weeks, at doses up to 500 mg/kg/day in rats and 1000 mg/kg/day in mice, revealed no evidence of carcinogenic potential. The maximum doses administered in both rat and mouse studies were, on a systemic exposure basis, less than the human exposure at the MRHD of the drug. *Cilostazol* tested negative in bacterial gene mutation, bacterial DNA repair, mammalian cell gene mutation, and mouse *in vivo* bone marrow chromosomal

aberration assays. It was, however, associated with a significant increase in chromosomal aberrations in the *in vitro* Chinese Hamster Ovary Cell assay.

Cilostazol did not affect fertility or mating performance of male and female rats at doses as high as 1000 mg/kg/day. At this dose, systemic exposures (AUCs) to unbound *cilostazol* were less than 1.5 times in males, and about 5 times in females, the exposure in human at the MRHD.

Use In Children

The safe use of PLETAAL in premature babies, newborns, suckling infants, infants, and children has not been established. (Clinical experience in these populations is insufficient).

Use In Elderly

Pharmacokinetic studies have not disclosed any age-related effects on the absorption, distribution, metabolism, and elimination of *cilostazol* and its metabolites. However, elderly patients may be physiologically more sensitive to PLETAAL than younger patients. It may be necessary to reduce the dosage when prescribing this drug to elderly patients.

ADVERSE REACTIONS

Adverse reactions, including abnormal laboratory tests, were reported in 436 (8.92%) of a total of 4890 patients receiving PLETAAL. The following adverse reactions include those reported without information concerning frequency of occurrence after the drug was placed on the market. (Figures are total cases reported from the time of initial approval up to the completion of reexamination and approval of the additional indication.

Clinically Significant Adverse Reactions

Congestive heart failure, myocardial infarction, angina pectoris, and ventricular tachycardia: Congestive heart failure, myocardial infarction, angina pectoris, and ventricular tachycardia may occur. If any signs of these adverse reactions are observed, the drug should be discontinued and appropriate corrective measures taken.

(Note: In a clinical study to evaluate PLETAAL's efficacy in the prevention of recurrence of cerebral infarction, angina pectoris [regardless of drug relationship] was reported in 6 of 516 [1.16%] patients.

Bleeding tendency: A tendency for abnormal bleeding, including cerebral hemorrhage, pulmonary hemorrhage (frequency unknown), hemorrhage in the digestive tract, epistaxis, and bleeding in the ocular fundus (less than 0.1%) may occur. If any signs of bleeding are observed, the drug should be discontinued and appropriate corrective measures taken.

Pancytopenia, agranulocytosis (frequency unknown), and thrombocytopenia (less than 0.1%): Pancytopenia, agranulocytosis, and thrombocytopenia may occur. Patients should be closely monitored. If any signs of these adverse reactions are observed, the drug should be discontinued and appropriate corrective measures taken.

Interstitial pneumonia: (frequency unknown): Interstitial pneumonia accompanied by fever, cough, dyspnoea, abnormal chest X-rays, and eosinophilia may occur. If any signs of interstitial pneumonia are noted, the drug should be discontinued and appropriate corrective measures, including adrenocorticotrophic hormone administration, should be taken.

Hepatic dysfunction (0.1% to less than 5%) and jaundice (frequency unknown): Hepatic function, as indicated by elevated AST (GOT), ALT (GPT), Al-P, or LDH, and jaundice may occur. Patients should be closely monitored. If signs of hepatic dysfunction are observed, the drug should be discontinued and appropriate corrective measures taken.

Other Adverse Reactions

The following adverse reactions have been reported with a frequency of 0.1% to < 5%:

Hypersensitivity¹: Rash

Cardiovascular²: Palpitation, tachycardia and hot flushes.

Psychoneurological²: Headache/dull headache, dizziness, insomnia and numbness.

(In a clinical study to evaluate PLETAAL's efficacy in the prevention of recurrence of cerebral infarction, incidences of "headache and dull headache" and "palpitation" were respectively 63/520 [12.1%] and 27/520 [5.2%].

Gastrointestinal: Abdominal pain, nausea, vomiting, anorexia, diarrhea, heartburn and abdominal distention.

Bleeding tendency: Subcutaneous hemorrhage.

Hepatic: Increase in AST (GOT), ALT (GPT), alkaline phosphatase, and LDH.

Others: sweating, edema, and chest pain.

The following adverse reactions have been reported with a frequency of < 0.1%:

Hypersensitivity¹: Eruption, urticaria, and pruritus.

Cardiovascular²: Blood pressure increase.

Psychoneurological²: Sleepiness and tremor.

Hematological: Anemia, leucopenia.

Bleeding tendency: Hematuria.

Renal: Increase in blood urea nitrogen, creatinine and uric acid.

Others: Blood sugar increase, tinnitus, pain, malaise, weakness, conjunctivitis, increased micturition frequency, and fever.

The following adverse reactions have been reported with an unknown frequency:

Hypersensitivity¹: Photosensitivity.

Cardiovascular²: Arrhythmias, including atrial fibrillation, supraventricular tachycardia, supraventricular extrasystoles, and blood pressure decrease.

(¹If such signs or symptoms are observed, the drug should be discontinued).

(²If such signs or symptoms are observed, dosage reduction, discontinuation of the drug, or other appropriate corrective measures should be taken).

DRUG INTERACTIONS

PLETAAL is extensively metabolized by hepatic cytochrome P-450 (CYP) isoenzymes, mainly CYP3A4 and to a lesser extent, CYP2D6 and CYP2C19. Caution should be exercised when PLETAAL is coadministered with inhibitors of drug metabolizing enzyme CYP3A4 such as: macrolide antibiotics (e.g. erythromycin), HIV protease inhibitors (e.g. ritonavir), azole antimycotics (e.g. itraconazole and miconazole), cimetidine, diltiazem, and grapefruit juice, or with inhibitors of drug metabolizing enzyme CYP2C19 (e.g. omeprazole).

The effects of PLETAAL may be potentiated when it is used in combination with these drugs. PLETAAL should be reduced in dosage or started at a lower dose when coadministered with these drugs. Patients should be cautioned not to drink grapefruit juice while receiving PLETAAL.

Blood concentrations of *cilostazol* are increased when PLETAAL is coadministered with drugs or grapefruit juice components that inhibit the drug metabolizing enzyme CYP3A4 or CYP2C19. (see CLINICAL PHARMACOLOGY, *Pharmacokinetic and Pharmacodynamic Drug-Drug Interactions*).

PLETAAL should be administered with care when coadministered with the following drugs:

Anticoagulants (e.g., warfarin, Antiplatelet drugs (e.g., aspirin and ticlopidine), Thrombolytic drugs (e.g., urokinase and alteplase) and Prostaglandin E₁ or its derivatives (e.g., alprostadil and limaprost alfadex).

Since PLETAAL has an inhibitory effect on platelet aggregation, coadministration with these drugs may increase bleeding tendency.

If bleeding occurs, bleeding tendency may be increased. Coagulation tests or other appropriate monitoring procedures should be employed when PLETAAL is used in

combination with these drugs in order to minimize the risk of adverse reactions such as hemorrhage.

OVERDOSAGE

Information on acute overdosage with PLETAAL 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.

CLINICAL PHARMACOLOGY

Mechanism of Action

PLETAAL 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 vascular smooth muscle, leading to inhibition of platelet aggregation and vasodilation. The mechanism of the effects of PLETAAL on the ischemic symptoms in chronic arterial occlusion and the symptoms of intermittent claudication is not fully understood.

Experiments in rabbits showed that *cilostazol* suppressed serotonin release from platelets without affecting serotonin and adenosine uptake by platelets. The drug inhibited platelet aggregation induced by thromboxane A₂ (TXA₂).

Cilostazol's antiaggregation effect in human platelets was augmented in the presence of vascular endothelial cells prostaglandin E₁.

Cilostazol's antiaggregation effect in canine platelets was augmented in the presence of prostaglandin I₂ or adenosine.

Antiplatelet Action

In Vitro Studies

- *Cilostazol* inhibited platelet aggregation induced by ADP, collagen, arachidonic acid, epinephrine, and thrombin, in humans.
- *Cilostazol* inhibited ADP or epinephrine-induced primary aggregation and exhibited a dispersing effect on platelet aggregates induced by various aggregating agents.
- *Cilostazol* inhibited thromboxane A₂ production in activated human platelets.
- *Cilostazol* inhibited procoagulant activity of human platelets.

In Vivo studies

- *Cilostazol* inhibited ADP and collagen-induced platelet aggregation when orally administered to beagle dogs and pigs.
- The inhibitory effect of *cilostazol* on ADP-induced platelet aggregation was unchanged during repeated oral administration in rats.
- *Cilostazol* prevented platelet aggregation induced by ADP, collagen, arachidonic acid, and epinephrine when orally administered to patients with chronic arterial occlusion or cerebral infarction.
- The onset of the platelet aggregation inhibitory effect of *cilostazol* was prompt in humans, and the effect is persistent even when administration was repeated.
- Following the discontinuation of *cilostazol* administration, the suppression of platelet aggregability returned to baseline levels without any rebound phenomenon (enhancement of platelet aggregation) as the plasma concentration of the drug declined.

Antithrombotic Action

Cilostazol reduced mortality due to pulmonary embolism induced experimentally in mice by the intravenous administration of ADP or collagen. The drug suppressed the

progression of peripheral thrombotic circulatory insufficiency in the hind limbs induced by the intra-arterial injection of sodium laurate solution into the femoral artery of dogs. The drug inhibited thrombotic occlusion of prosthetic artificial grafts placed in the femoral artery of dogs.

Cilostazol inhibited electrical stimulation-induced thrombus formation in the carotid artery of pigs.

Cilostazol reduced the size of cerebral infarction induced by injection of arachidonic acid into the internal carotid artery of rabbits.

Cilostazol reduced the frequency of ischemic attacks in patients with transient ischemic attacks.

Cardiovascular Effects

Cilostazol inhibited KCl and prostaglandin $F_{2\alpha}$ - induced contraction of the isolated femoral, middle cerebral, and basilar, arteries in dogs.

Cilostazol increased blood flow in the femoral, vertebral, common carotid, and internal carotid arteries in anesthetized dogs.

Cilostazol increased blood flow in the cerebral cortex in anesthetized dogs and cats.

Cilostazol increased blood flow in the cerebral cortex and hypothalamus in conscious rats.

The results of a plethysmographic study showed that the drug increased blood flow in the occluded ankle and calf region in patients with chronic arterial occlusion. The results of the thermographic plethysmographic study demonstrated that the drug induced an increase in the skin temperature of the extremities and an increase in cutaneous blood flow in patients with chronic arterial occlusion.

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 100mg 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.

Cilostazol increased cerebral blood flow in patients with ischemic cerebrovascular diseases, as determined by the xenon-inhalation method.

Effects on Vascular Cells

Cilostazol suppressed ³H-thymidine uptake in cultured human vascular smooth muscle cells.

Cilostazol suppressed the depletion of lactate dehydrogenase from cultured human endothelial cells stimulated with homocysteine or lipopolysaccharide.

PHARMACOKINETICS

Plasma Concentrations

PLETAAL is absorbed after oral administration. Following the single oral administration of *cilostazol* at 100 mg to fasted normal healthy individuals, the plasma concentration promptly rose to a maximum level of 763.9 ng/ml in 3 hours. The plasma half-life of the drug estimated using a two-compartment model was 2.2 hours in the α -phase and 18.0 hours in the β -phase. Two metabolites were found to be active: OPC-13015 (dehydrated metabolite) and OPC-13213 (hydroxylated metabolite). Administration in the fed state was associated with a 2.3-fold increase in the C_{max} and 1.4-fold increase in the AUC,

compared with administration in the fasting state, following a single oral dose of 50 mg (from Japanese studies). 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.

Protein Binding

Cilostazol: Greater than 95% (equilibrium dialysis *in vitro*, 0.1-6 µg/mL).

Active metabolite OPC-13015: 97.4% (ultrafiltration *in vitro*, 1 µg/mL).

Active metabolite OPC-13213: 53.7% (ultrafiltration *in vitro*, 1 µg/mL).

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 100mg 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 the urine (74%), with the remainder excreted in the 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 the 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 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: Plasma concentrations of *cilostazol* following single oral administration of PLETAAL at a dose of 100 mg in patients with mild to moderate hepatic impairment were similar (C_{max} decreased by 7% and AUC increased by 8%) to those in normal healthy individuals.

Renal Impairment: Repeated oral administration of PLETAAL at a daily dose of 100 mg for 8 days in patients with severe renal impairment showed decreases (C_{max} by 29% and AUC by 39%) in plasma concentrations of the active metabolite OPC-13213 compared with administration in normal healthy individuals. However, the concentrations of *cilostazol* and OPC-13213 in patients with mild to moderate renal impairment were similar to those in normal healthy individuals. 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%).

Pharmacokinetic and Pharmacodynamic Drug-Drug Interactions

Cilostazol could have pharmacodynamic interactions with other inhibitors of platelet function and pharmacokinetic interactions because of effects of other drugs on its metabolism by CYP3A4 or CYP2C19.

Aspirin: Short-term (≤ 4 days) coadministration of aspirin with PLETAAL showed a 23-35% increase in inhibition of ADP-induced *ex vivo* platelet aggregation compared to aspirin alone; there was no clinically significant impact on PT, aPTT, or bleeding time compared to aspirin alone. There was no additive or synergistic effect on arachidonic acid-induced platelet aggregation. Effects of long-term coadministration in the general population are unknown. In eight randomized, placebo-controlled, double-blind clinical trials, aspirin was coadministered with *cilostazol* to 201 patients. The most frequent doses and mean durations of aspirin therapy were 75-81 mg daily for 137 days (107 patients) and 325mg daily for 54 days (85 patients). There was no apparent greater incidence of

hemorrhagic adverse effects in patients taking *cilostazol* and aspirin compared to patients taking placebo and equivalent doses of aspirin.

Clopidogrel: Coadministration significantly increased AUC of dehydro-cilostazol metabolite by 24%. Although it cannot be determined whether there was an additive effect on bleeding times during concomitant administration with *cilostazol* and clopidogrel, caution is advised for checking bleeding times at intervals during coadministration of *cilostazol* and clopidogrel.

Warfarin: The cytochrome P-450 isoenzymes involved in the metabolism of R-warfarin are CYP3A4, CYP1A2, and CYP2C19, and in the metabolism of S-warfarin, CYP2C9. PLETAAL did not inhibit either the metabolism or the pharmacologic effects (PT, aPTT, bleeding time, or platelet aggregation) of R- and S-warfarin when administered in combination with a single dose of warfarin 25 mg. The effect of concomitant multiple dosing of warfarin and PLETAAL on the pharmacokinetics and pharmacodynamics of both drugs is unknown.

Omeprazole: Coadministration of a single dose of *cilostazol* 100 mg during repeated administration of omeprazole 40 mg qd for 7 days increased *cilostazol* C_{max} by 18% and AUC by 26% compared with administration of *cilostazol* alone.

Erythromycin and other macrolide antibiotics: Erythromycin is a moderately strong inhibitor of CYP3A4. Coadministration of erythromycin 500 mg q 8h for 7 days with a single dose of *cilostazol* 100 mg increased *cilostazol* C_{max} by 47% and AUC by 87%. 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: Diltiazem is a moderate inhibitor of CYP3A4. Coadministration of diltiazem 180 mg with a single dose of *cilostazol* 100 mg increased *cilostazol* C_{max} by 34% and AUC by 44% compared with administration of *cilostazol* alone.

Quinidine: Concomitant administration of quinidine with a single dose of *cilostazol* 100mg did not alter *cilostazol* pharmacokinetics.

Ketoconazole: Coadministration of a single dose of ketoconazole 400 mg with a single dose of *cilostazol* 100 mg increased *cilostazol* C_{max} by 94% and AUC by 129% compared with administration of *cilostazol* alone.

Lovastatin: Coadministration of a single dose of lovastatin 80 mg with a single dose of PLETAAL 100 mg increased lovastatin AUC by 64% compared with administration of lovastatin alone.

Grapefruit Juice: Administration of a single dose of *cilostazol* 100 mg with 240 mL of grapefruit juice increased *cilostazol* C_{max} by 46% and AUC by 14% compared with administration of *cilostazol* without grapefruit juice.

CLINICAL STUDIES

PLETAAL Tablets were studied in a total of 226 patients with chronic arterial occlusive disease in open and double-blind studies. Based on global judgement, the drug was judged to be either effective or very effective on ischemic symptoms, including ulcerations, pain, and coldness of the extremities, in 67.2% (131/195) of the patients with peripheral circulatory insufficiency, and judged to be slightly effective or better in 85.6% (167/195) of patients with peripheral circulatory insufficiency.

The ability of PLETAAL to improve walking distance in patients with stable intermittent claudication was studied in eight large, randomized, placebo-controlled, double-blind trials of 12 to 24 weeks' duration using dosages of 50 mg b.i.d. (n=303), 100 mg b.i.d. (n=998), and placebo (n=973). Efficacy was determined primarily by the change in maximal walking distance from baseline (compared to change on placebo) on one of several standardized exercise treadmill tests.

Compared to patients treated with placebo, patients treated with PLETAAL 50 or 100mg b.i.d. experienced statistically significant improvement in walking distances both for the distance before the onset of claudication pain and the distance before exercise-limiting symptoms supervened (maximal walking distance). The effect of PLETAAL on walking distance was seen as early as the first on-therapy observation point of two or four weeks.

Across the eight clinical trials, the range of improvement in maximal walking distance in patients treated with PLETAAL 100mg b.i.d., expressed as the percent mean and median change from baseline, was 28 to 100% and 17% to 72%, respectively. The corresponding changes in the placebo group were – 10 to 30% and –2 to 29% respectively.

PLETAAL tablets were studied in a total of 1034 patients with cerebral infarction in a placebo-controlled double-blind study. The annual incidence rates of cerebral infarction were 3.43% and 5.75% in the PLETAAL and placebo groups, respectively (total duration of observation: 873.8 and 973.7 person-years; incidence of recurrence: 30 and 56). The estimated risk reduction per person-year for PLETAAL treatment relative to placebo treatment was 40.3%. Based on the number of “all-cause deaths” during the treatment period (one of the secondary endpoints) the annual mortality rates in the PLETAAL and placebo groups were estimated to be respectively 0.92% and 0.82%, showing no significant difference between the two groups. In this study, occurrence of angina pectoris was reported in more patients in the PLETAAL group (6/516) than in the placebo group (0/518).

PHARMACEUTICAL PRECAUTIONS

Store at room temperature, protect from moisture and sunlight.

Keep all medicines out of the reach of children.

Do not use after the expiration date indicated on the package.

PLETAAL is a prescription drug only.

HOW SUPPLIED

PLETAAL is supplied as 50-mg and 100-mg tablets in packs of 30 tablets (blister strips of 10 x 3). The 50-mg tablets are white, round, debossed with OG31. The 100-mg tablets are white, round, debossed with OG30.

Tablets manufactured by **Otsuka Pharmaceutical Co. Limited, Tokyo, Japan.**

Packed by **Efroze Chemical Industries (Pvt.) Limited, for Otsuka Pakistan Limited.**