- ANTIPLATELET AGENT -

PLETAAL® Tablets 50 mg
PLETAAL® Tablets 100 mg

< Cilostazol >

Designated Drug and Prescription-only Drug

Storage: Store below 30℃.

Expiration date: Three years after the date of manufacture. (The expiration date is indicated on the package.)

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. Pletaal is contraindicated in patients with congestive heart failure of any severity. Pletaal is contraindicated in patients with haemostatic disorders or active pathologic bleeding, such as bleeding peptic ulcer and intracranial bleeding. Pletaal inhibits platelet aggregation in a reversible manner. Pletaal is contraindicated in patients with known or suspected hypersensitivity to any of its components.

DESCRIPTION

1. Composition

Each tablet of **PLETAAL Tablets 50 mg** contains 50 mg of cilostazol and the following inactive ingredients: microcrystalline cellulose, corn starch, carboxymethyl cellulose calcium, hydroxypropyl methyl cellulose 2910, and magnesium stearate.

Each tablet of **PLETAAL Tablets 100 mg** contains 100 mg of cilostazol and the following inactive ingredients: microcrystalline cellulose, corn starch, carboxymethyl cellulose calcium, hydroxypropyl methyl cellulose 2910, and magnesium stearate.

2. Product Description

Pletaal Tablets are white compressed tablets.

	Appearance	Diame-ter (mm)	Thick-ness (mm)	Weight (mg)	Code
PLETAAL Tablets 50 mg		7	2.5	Approx. 115	OG31
PLETAAL Tablets 100 mg		8	3.0	Approx. 170	OG30

INDICATIONS

Pletaal is indicated for the improvement of the maximal and pain-free walking distances in patients with intermittent claudication, who do not have rest pain and who do not have evidence of peripheral tissue necrosis.

Pletaal is indicated for prevention of recurrence of cerebral infarction (excluding cardiogenic cerebral embolism). The effects of PLETAAL on cerebral infarction have not been studied in patients with asymptomatic cerebral infarction.

DOSAGE AND ADMINISTRATION

The recommended dosage of Pletaal is 100 mg b.i.d. taken at least half an hour before or two hours after breakfast and dinner. A dose of 50 mg b.i.d. should be considered during coadministration of such inhibitors of CYP3A4 as ketoconazole, itraconazole, erythromycin and diltiazem, and during coadministration of such inhibitors of CYP2C19 as omeprazole.

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 Pletaal can be reduced or discontinued without rebound (i.e., platelet hyperaggregability).

PRECAUTIONS

Pletaal is contraindicated in patients with congestive heart failure. In patients without congestive heart failure, the long-term effects of PDE III inhibitors (including Pletaal) are unknown. Patients in the 3-6 month placebo-controlled trials of Pletaal were relatively stable (no recent myocardial infarction or strokes, no rest pain or other signs of 0.8% in the group on Pletaal). The calculated relative risk of death of 1.2 has a wide 95% confidence limit (0.5-3.1). There are no data as to longer-term risk or risk in patients with more severe underlying heart disease.

Use in patients at risk of bleeding or with other antiplatelet agents: Pletaal inhibits platelet aggregation but in a reversible manner. Caution is advised in patients at risk of bleeding from

surgery or pathologic processes. Platelet aggregability returns to normal within 96 hours of stopping Pletaal.
Caution is advised in patients with thrombocytopenia.
Cautions should also be exercised for patients treated concomitantly with two or more additional antiplatelet or anticoagulant agents (e.g acetylsalicylic acid, clopidogrel, heparin, warfarin, acenocoumarol, dabigatran, rivaroxaban or apixaban) for increased potential risk of bleeding.

Hematologic adverse reactions: Caution is advised in patients with thrombocytopenia.Rare cases have been reported of thrombocytopenia or leukopenia progressing to agranulocytosis when cilostazol was not immediately discontinued. The agranulocytosis, however, was reversible on discontinuation of cilostazol. Patients under long-term use of Pletaal should be monitored periodically for any signs or symptoms of decreased white blood cell count and / or platelet count.

Use with Clopidogrel.
There is limited 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.. Although it cannot be determined whether there was an additive effect on bleeding times during concomitant administration with cilostazol and clopidgrel, caution should be advised for checking bleeding times during coadministration.

Information for Patients:
Patients should be advised:
- to read the patient package insert for Pletaal carefully before starting therapy and to reread it each time therapy is renewed in case the information has changed.
- to take Pletaal at least one-half hour before or two hours after food.
- that the beneficial effects of Pletaal on the symptoms of intermittent claudication may not be immediate. Although the patient may experience benefit in 2 to 4 weeks after initiation of therapy, treatment for up to 12 weeks may be required before a beneficial effect is experienced.
- about the uncertainty concerning cardiovascular risk in long-term use or in patients with severe underlying heart disease, as described under PRECAUTIONS.

Severe Hepatic Impairment:
Patients with moderate or severe hepatic impairment have not been studied in clinical trials.
Special caution should be advised when Pletaal is used in patients with severe hepatic impairment.

Severe 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 (95-98%).
Special caution should be advised when Pletaal is used in patients with severe renal impairment: creatinine clearance ≤ 25 ml/min.

Cardiovascular
Events of left ventricular outflow tract obstruction have been reported in patients with sigmoid shaped interventricular septum. Pletal/Pletaal should be used with caution in patients at risk, especially in elderly patients. Additional tests or an echocardiogram can be performed if the patient develops a de novo cardiac murmur after starting cilostazol
Based on its mechanism of action, cilostazol may induce tachycardia, palpitation, tachyarrhythmia and/or hypotension. The increase in heart rate associated with cilostazol isapproximately 5 to 7 bpm; in patients at risk this consequently may induce angina pectori.
Special caution should be used for patients with a history of tachyarrhythmia who are being treated for intermittent claudication. Cilostazol should be initiated by physicians experienced in the management of intermittent claudication.
The physician should reassess the patient after 3 months of treatment with a view to discontinuing cilostazol where an inadequate effect is observed or symptoms have not been improved .
Also precautions must be used for patients with unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months who are being treated for intermittent claudication. Patients receiving treatment with cilostazol should continue with their life-style modifications (smoking cessation and exercise), and pharmacological interventions (such as lipid lowering and antiplatelet treatment) to reduce the risk of cardiovascular events.
A significant increase in PRP (pressure rate product) was observed during long-term administration of Pletaal in a study conducted in Japan to evaluate the drug's efficacy in the prevention of recurrence of cerebral infarction. Increased pulse rate possibly resulting from the treatment with cilostazol could induce angina pectoris in patients with coronary artery stenosis.

Interaction with Food and with Other Drugs:

Food effect: A high-fat meal increased absorption of cilostazol, with an approximately 90% increase in Cmax and a 25% increase in AUC.

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.
Aspirin: Short term (≤4 days) co-administration of Pletaal and aspirin resulted in small increases of plasma levels of cilostazol and its active metabolites together with 23-37%

increase in inhibition of ADP induced *ex vivo* platelet aggregation compared to that obtained with either aspirin or Pletaal alone.

Short term (≤4 days) co-administration of aspirin with Pletaal increased the inhibition of arachidonic acid-induced *ex vivo* platelet aggregation by 20% compared to Pletaal alone, and by 48% compared to aspirin alone. However, short-term (≤4 days) co-administration of aspirin with Pletaal had no clinically significant impact on PT, PTT, or bleeding time compared to aspirin alone.

Warfarin: The pharmacokinetics and the effects on prothrombin time of a single 25mg dose of warfarin were not affected by twice daily administration of Pletaal 100mg. However, caution is advised in patients receiving both cilostazol and any anticoagulant agent.

Cytochrome P-450 (CYP) Enzyme Inhibitors:

Cilostazol is extensively metabolized by **hepatic cytochrom P450** (CYP) enzymes, mainly CYP3A4, and to lesser extent by CYP2C19. Inhibitors of CYP3A4, such as itraconazole, erythromycin, diltiazem, and ketoconazole; and the inhibitors of CYP2C19 such as omeprazole, have been shown to increase blood levels of cilostazol and / or its metabolites. Cilostazole had little effect on blood levels of lovastatin which is highly sensitive to CYP3A4 inhibition.

CYP3A4 Inhibitors:

Grapefruit juice Administration of a single dose of 100mg cilostazol with 240mL grapefruit juice (an inhibitor of intestinal CYP3A4) did not have a notable effect on the pharmacokinetics of cilostazol. Based on these data, no dose adjustment is necessary. A clinically relevant effect on cilostazol is still possible at higher quantities of grapefruit juice.

Ketoconazole Co-administration of ketonazole (an inhibitor of CYP3A4) with cilostazol resulted in a 117% increase in the AUC of cilostazol, accompanied by a 15% decrease in the AUC of the dehydro metabolite and an 87% increase in the AUC of the 4'-trans-hydroxy metabolite. Based on AUC, the overall pharmacological activity of cilostazol increases 35% when co-administered with ketoconazole. Based on these data, the recommended dose of cilostazol is 50mg bid in the presence of ketoconazole and similar agents (e.g., intraconazole).

Diltiazem:

Administration of cilostazol with diltiazem resulted in an increase in the AUC of cilostazol by 44%, accompanied by a 4% increase in AUC of the dehydro metabolite and a 43% increase in the AUC of the 4'-trans-hydroxy metabolite.

Based on AUC, overall pharmacological activity of cilostazol increases by 19% when co-administered with diltiazem. Based on these data, the recommended dose of cilostazol is 50mg bid in the presence of diltiazem.

Erythromycin: Administration of cilostazol with erythromycin resulted in an increase in the AUC of cilostazol by 72%, accompanied by a 6% increase in AUC of the dehydro metabolite and a 119% increase in AUC of the 4'-trans-hydroxy metabolite. Based on AUC, the overall pharmacological activity of cilostazol increases by 34% when co-administered with erythromycin. Based on these data, the recommended dose of cilostazol is 50mg bid in the presence of erythromycin and similar agents (e.g., clarithromycin).

CYP2C19 Inhibitors:

Omeprazole: Administration of cilostazol with omeprazole (an inhibitor of CYP2C19) increased the AUC of cilostazol by 22%, accompanied by a 68% increase in the AUC of the dehydro metabolite and a decrease of 36% in the AUC of the 4'-trans hydroxyl metabolite. Based on AUC, the overall pharmacological activity increases by 47% when co-administered with omeprazole. Based on these data, the recommended dose of cilostazol is 50mg bid in the presence of omeprazole.

CYP2D6 Inhibitors:

Quinidine: (CYP2D6 inhibitor) A 200mg single dose of quinidine had no significant effect on the pharmacokinetics of a single 100mg dose of cilostazol.

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). At this dose, systemic exposure to unbound cilostazol in nonpregnant rats was about 5 times the exposure in humans given the MRHD. Increased incidences of ventricular septal defect and retarded ossification were also noted at 150 mg/kg/day (5 times the MRHD on a 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 Mothers:

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 Pletaal.

Pediatric Use:
The safety and effectiveness of Pletaal in pediatric patients have not been established.

Geriatric Use:
Of the total number of subjects (n = 2274) in clinical studies of Pletaal, 56 percent were 65-years-old and over, while 16 percent were 75-years-old and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Pharmacokinetic studies have not disclosed any age-related effects on the absorption, distribution, metabolism, and elimination of cilostazol and its metabolites.

Effects on Ability to Drive Vehicles and Operate Machinery:
There are no controlled studies of the effects Pletaal on driving performance. Some patients have reported dizziness or vertigo while on Pletaal, and such patients should be cautioned against driving or operating machinery.

UNDESIRABLE EFFECTS
Clinical Study Data:
Peripheral Arterial Disease
Table 1 shows the adverse experiences reported during placebo-controlled clinical trials of Pletaal at 50 or 100mg twice a day for 12 to 24 weeks. Included are adverse experiences that occurred in ≥2% of patients and, at 100mg twice a day, occurred at a higher rate than with placebo and are considered to have a causal relationship based on the mechanism of action or previous findings.
Table 1 lists the types of adverse events reported with Pletaal exposure, although varying incidence rates were observed in similar clinical studies conducted in different geographic areas. The incidence rates in Table 1 represent that which was observed in the trials conducted in the United States, which were the highest rates observed over all clinical trials.

Table 1. Undesirable Effects Observed in Pletaal Clinical Studies

Undesirable Effect by Body System	Pletaal 50mg twice a day (N=303) %	Pletaal 100mg twice a day (N=998) %	Placebo (N=973) %
NERVOUS SYSTEM DISORDERS			
Headache Dizziness	27 9	34 10	14 6
CARDIAC DISORDERS			
Palpitation Tachycardia	5 4	10 4	1 1
GASTROINTESTINAL DISORDERS			
Diarrhea Dyspepsia Flatulence	12 6 2	19 6 3	7 4 2
Nausea Abdominal Pain	6 4	7 5	6 3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Peripheral edema	9	7	4

Prevention of stroke recurrence
Table 2 lists adverse drug reactions (ADRs) reported during post-marketing study of Pletaal in Japan. Included are ADRs that occurred with a significantly higher rate in patients treated with Pletaal that in Aspirin.

Table 2. Undesirable Effects Observed in Pletaal Post-marketing Study

Undesirable Effect By System Organ Class	Pletaal 100mg twice a day (N=1337) %	Aspirin 81mg once a day (N=1335) %
NERVOUS SYSTEM DISORDERS		
Headache	15.6	4.4
Dizziness	1.6	0.7
CARDIAC DISORDERS		
Palpitation	9.7	1.2
Tachycardia	5.5	0.4
Sinus tachycardia	2.9	0.6
Arrhythmia	0.7	0
GASTROINTESTINAL DISORDERS		
Diarrhoea	1.6	0.7
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Chest discomfort	0.7	0.1
Pyrexia (Fever)	0.4	0
INVESTIGATIONS		
Blood glucose increased	0.5	0.1
Heart rate increased	0.5	0

Other Post-marketing Data
Table 3 shows the additional ADRs to Pletaal not included in the clinical studies tables (Table 1 and 2), reported spontaneously during the post-marketing period. The exact rate of these spontaneously reported ADRs is unknown.

Table 3. Post-marketing Undesirable Effects

System Organ Class	Adverse Reactions
Infections and infestations	Interstitial pneumonia
Blood and lymphatic system disorders	Agranulocytosis Anaemia Bleeding tendency Granulocytopenia Leukopenia Pancytopenia Thrombocytopenia
Metabolism and nutrition disorders	Anorexia
Psychriatric disorders	Insomnia
Nervous system disorders	Cerebral haemorrhage
Eye disorders	Conjunctivitis

	Retinal haemorrhage
Ear and labyrimth disorders	Tinnitus
Cardiac disorders	Angina pectoris Atrial fibrillation Congestive heart failure Myocardial infarction Supraventricular tachycardia Ventricular extrasystoles Ventricular tachycardia
Vascular disorders	Hot flushes Hypertension Hypotension
Respiratory, thracic and mediastinal disorders	Epistaxis Pulmonary haemorrhage
Gastrointestinal disorders	Gastrointestinal haemorrhage Melena Vomiting
Hepatobiliary disorders	Hepatic function abnormal Jaundice
Skin & subcutaneous tissue disorders	Haemorrhage subcutaneous Pruritus Rash Skin drug eruptions Urticaria
General disorders and administration site conditions	Chest pain Oedema generalized Malaise Pain
Renal and urinary disorders	Hematuria Pollakiuria (Urinary frequency)
Investigations	Blood creatinine increased (Increased creatinaemia) Blood pressure decreased Blood pressure increased Blood urea increased Blood uric acid increased Platelet count decreased White blood cell count decreased

PHARMACOKINETICS

1. Plasma Concentrations

Following single oral administration of cilostazol 100 mg to fasted normal healthy individuals, the plasma cilostazol 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 of a single oral dose of cilostazol 50 mg in a fed state was associated with a 2.3-fold increase in Cmax and a 1.4-fold increase in AUC_{inf} compared with administration in a fasted state.

2. Metabolizing Enzymes

Cilostazol is extensively metabolized by hepatic cytochrome P-450 enzymes, mainly CYP3A4, and to a lesser extent, CYP2D6 and CYP2C19 (*in vitro*).

3. 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)

4. Pharmacokinetics in Patients with Renal Impairment (Outside Japan)

Repeated oral administration of Pletaal at a daily dose of 100 mg for 8 days in patients with severe renal impairment showed decreases (Cmax by 29% and AUC by 39%) in plasma concentrations of cilostazol and marked increases (Cmax by 173% and AUC by 209%) 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.

5. Pharmacokinetics in Patients with Hepatic Impairment (Outside Japan)

Plasma concentrations of cilostazol following single oral administration of Pletaal 100 mg in patients with mild to moderate hepatic impairment were similar (Cmax decreased by 7%, AUC increased by 8%) to those in normal healthy individuals.

6. Drug Interactions (Outside Japan)

Pletaal did not inhibit either the metabolism or pharmacological effects of R- and S-warfarin when administered in combination with a single dose of warfarin 25 mg.

Coadministration of a single dose of cilostazol 100 mg during repeated administration of erythromycin 500 mg tid for 7 days increased cilostazol Cmax by 47% and AUC by 87% compared with administration of cilostazol alone.

Coadministration of a single dose of ketoconazole 400 mg with a single dose of cilostazol 100 mg increased cilostazol Cmax by 94% and AUC by 129% compared with administration of cilostazol alone. (The oral formulation of the azole antimycotic ketoconazole has not yet been approved in Japan.)

Coadministration of diltiazem 180 mg with a single dose of cilostazol 100 mg increased cilostazol Cmax by 34% and AUC by 44% compared with administration of cilostazol alone.

Administration of a single dose of cilostazol 100 mg with 240 mL of grapefruit juice increased cilostazol Cmax by

46% and AUC by 14% compared with administration of cilostazol without grapefruit juice.

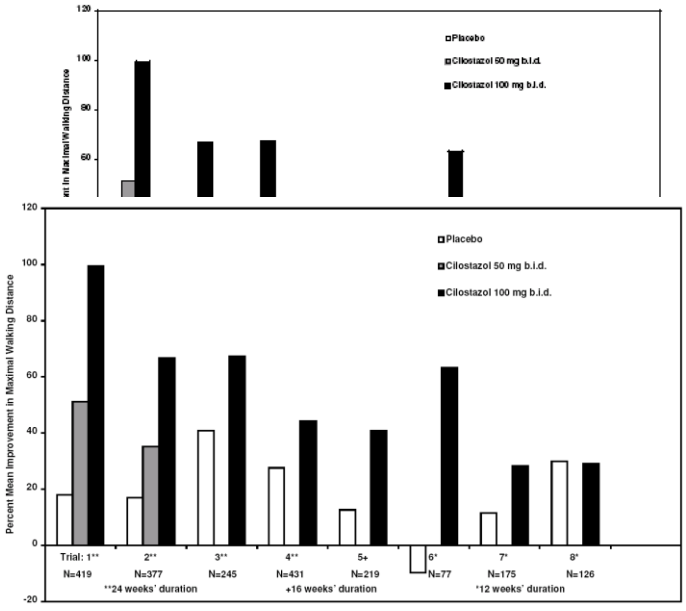
Coadministration of a single dose of cilostazol 100 mg during repeated administration of omeprazole 40 mg qd for 7 days increased cilostazol Cmax by 18% and AUC by 26% compared with administration of cilostazol alone.

CLINICAL STUDIES

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 100 mg b.i.d. experienced statistically significant improvements 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.

The following figure depicts the percent mean improvement in maximal walking distance, at study end for each of the eight studies.



Across the eight clinical trials, the range of improvement in maximal walking distance in patients treated with Pletaal 100 mg b.i.d., expressed as the percent mean change from baseline, was 28% to 100%.

The corresponding changes in the placebo group were –10% to 41%.

The Walking Impairment Questionnaire, which was administered in six of the eight clinical trials, assesses the impact of a therapeutic intervention on walking ability. In a pooled analysis of the six trials, patients treated with either Pletaal 100 mg b.i.d. or 50 mg b.i.d. reported improvements in their walking speed and walking distance as compared to placebo. Improvements in walking performance were seen in the various subpopulations evaluated, including those defined by gender, smoking status, diabetes mellitus, duration of peripheral artery disease, age, and concomitant use of beta blockers or calcium channel blockers. Pletaal has not been studied in patients with rapidly progressing claudication or in patients with leg pain at rest, ischemic leg ulcers, or gangrene. Its long-term effects on limb preservation and hospitalization have not been evaluated. No reliable estimate of its effect on survival is available (see PRECAUTIONS).

PHARMACOLOGY

1. Antiplatelet Action

(1) *In vitro* studies

- Cilostazol inhibited platelet aggregation induced by ADP, collagen, arachidonic acid, epinephrine, and thrombin in humans. The drug also inhibited shear stress-induced platelet aggregation.
- Cilostazol inhibited ADP- and epinephrine-induced primary aggregation and exhibited a dispersing effect on human platelet aggregates induced by various aggregating agents.
- Cilostazol inhibited thromboxane A_2 production in activated human platelets.
- Cilostazol inhibited procoagulant activity of human platelets.

(2) *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 cilostazol's platelet aggregation inhibitory effect was prompt in humans, and the effect persisted during repeated administration.
- Following discontinuation of cilostazol administration, as the plasma concentration of the drug declined, platelet aggregability returned to baseline levels with no rebound phenomenon (no increase of platelet aggregation).

2. Antithrombotic Action

- Cilostazol reduced mortality due to pulmonary embolism induced experimentally in mice by intravenous administration of ADP or collagen.
- Cilostazol suppressed the progression of peripheral thrombotic circulatory insufficiency in the hind limbs induced by intra-arterial injection of sodium laurate solution into the femoral artery of dogs.
- Cilostazol 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.

3. Vasodilating Action

- 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.
- Results of a plethysmographic study showed that cilostazol increased blood flow in the occluded ankle and calf region in patients with chronic arterial occlusion, and results of a thermographic plethysmographic study demonstrated that the drug induced an increase in skin temperature of the extremities and increased cutaneous blood flow in patients with chronic arterial occlusion.
- Cilostazol increased cerebral blood flow in patients with ischemic cerebrovascular diseases, as determined by the xenon-inhalation method.

4. Effects on Vascular Cells

- Cilostazol suppressed ^{3}H-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.

5. Mechanism of Action

- 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 A_2 (TXA_2).
- Cilostazol exerts its antiplatelet and vasodilating actions by selectively inhibiting PDE3 (cGMP-inhibited PDE) in platelets and vascular smooth muscle.
- Cilostazol's antiaggregation effect in human platelets was augmented in the presence of vascular endothelial cells or prostaglandin E_1.
- Cilostazol's antiaggregation effect in canine platelets was augmented in the presence of prostaglandin I_2 or adenosine.

PHYSICOCHEMISTRY

Non-proprietary name

Cilostazol (JAN, INN and USAN)

Chemical name:

6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone

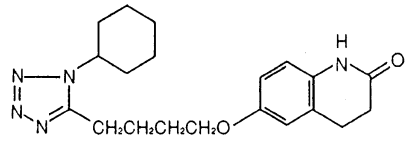
Molecular formula

$C_{20}H_{27}N_5O_2$

Molecular weight

369.46

Structural formula



Melting point

158-162°C

Description

Cilostazol occurs as white to pale yellowish white crystals or crystalline powder. It is odorless and tasteless. It is soluble in *N*,*N*-dimethylformamide and in benzyl alcohol, slightly soluble in methanol and in ethanol, and practically insoluble in water and in dehydrated ether.

PACKAGING

PLETAAL Tablets 50 mg:

Boxes of 100 tablets in press-through packages

PLETAAL Tablets 100 mg:

Boxes of 100 tablets in press-through packages

SYMPTOMS AND TREATMENT OF OVERDOSE

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 LD_{50} of cilostazol is >5.0 g/kg in mice and rats and >2.0 g/kg in dogs.

REQUESTS FOR LITERATURE SHOULD BE ADDRESSED TO:

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