- ANTIPLATELET AGENT -

PLETAAL® Tablets 50
PLETAAL® Tablets 100
PLETAAL® SR Capsule 100 mg

(Cilostazol)

COMPOSITION AND DESCRIPTION

Composition

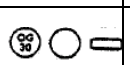
Each tablet of PLETAAL®Tablets 50 contains 50 mg of cilostazol. Each tablet of PLETAAL® Tablets 100 contains 100 mg of cilostazol.
Each capsule of PLETAAL® SR Capsules 100 mg contains 100 mg of cilostazol

List of excipients:

PLETAAL® TABLET 50
PLETAAL® TABLET 100
Carmellose Calcium
Magnesium Stearate
Microcrystalline Cellulose
Hypromellose
Corn Starch
Purified Water

PLETAAL® SR
Microcrystalline Cellulose
Polysorbate 80
Corn Starch
Hydrated Silicon Dioxide
Pregelatinized Starch
Citric Acid Anhydrate
Hypromellose Capsule
Methacrylic Acid-Methyl Methacrylate Copolymer
Purified Water

Product Description

Brand Name	Description	Appearance	Diameter (mm)	Thickness (mm)	Weight (mg)	Code
PLETAAL® Tablets 50	White compressed Tablets		7	2.5	Ca 115	OG31
PLETAAL® Tablets 100	White compressed Tablets		8	3.0	Ca 170	OG30
PLETAAL® SR capsules 100 mg	White capsules filled with white granules, imprinted "OG29" in black ink.		Approx. **18**	Approx. **6**	Approx. **206.8**	**OG29**

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)

CONTRAINDICATIONS (Cilostazol is contraindicated in the following patients.)

1. 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.)
2. Patients with congestive heart failure (Condition may be worsened.) (See item **(5)** under **2. Important Precautions**.).
3. Patients with a history of hypersensitivity to any ingredient of the drug.
4. Women who are pregnant or may possibly become pregnant (See **4. Use During Pregnancy, Delivery, or Lactation**.)

DOSAGE AND ADMINISTRATION

PLETAAL® Tablet

The usual adult dose of PLETAAL Tablets is 100 mg of Cilostazol, twice daily by the oral route. The dosage may be adjusted according to the age of the patients and the severity of symptoms.

PLETAAL® SR Capsules 100 mg

The usual adult dose of PLETAAL SR Capsules 100 mg is 200 mg of cilostazol, once daily, by the oral route. This drug is taken on an empty stomach without food.

PHARMACOLOGY

1. Antiplatelet Action

(1) *In vitro* studies

- Cilostazol inhibited platelet aggregation induced by ADP, collagen, arachidonic acid, adrenaline, and thrombin in humans. The drug also inhibited shear stress-induced platelet aggregation.
- Cilostazol inhibited ADP- and adrenaline -induced primary aggregation and exhibited a dispersing effect on human platelet aggregates induced by various aggregating agents.
- Cilostazol inhibited thromboxane A_2 (TXA_2) production in activated human platelets.
- Cilostazol inhibited the 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 adrenaline when

PLE-PI-0420-001.03

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 incidence 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 Smooth Muscle Cells
- Cilostazol suppressed the proliferation of vascular smooth muscle cells in cultured human vascular smooth muscle.
- Cilostazol suppressed intimal thickening of rat carotid arteries induced by intimal balloon injury.

5. Effects on Vascular Endothelial Cells
- Cilostazol augmented NO production by cultured human endothelial cells.
- Cilostazol suppressed injuries of cultured human endothelial cells.
- Cilostazol suppressed the depletion of lactate dehydrogenase from cultured human endothelial cells stimulated with homocysteine or lipopolysaccharide.

6. 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[25] or prostaglandin E_1.
- Cilostazol's antiaggregation effect in canine platelets was augmented in the presence of prostaglandin I_2 or adenosine.

PHARMACOKINETICS

1. Plasma Concentration

(1) 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-compartement 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).

(2) 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 fasted state.

(3) When PLETAAL SR capsule was administered orally to healthy adult male subjects at multiple dose of 200 mg as cilostazol in fasting condition for 5 days, the following pharmacokinetic parameters were obtained at steady state.(Table 1)

Table 1. Pharmacokinetic Parameters for Cilostazol Following Administration at Multiple dose of 200 mg for 5 days

Dosage form	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
PLETAAL SR capsule	2097±797	6.5±1.4	8.62±2.77

(4) Following single oral administration of cilostazol to healthy adult male subjects, two metabolites were found to be active: OPC-13015 (dehydrated metabolite) and OPC-13213 (hydroxylated metabolite)

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 cilostazol 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 cilostazol and marked increases (C_{max} 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 cilostazol 100 mg in patients with mild to moderate hepatic impairment were similar (C_{max} decreased by 7%, AUC increased by 8%) to those in normal healthy individuals.

6. **Drug Interactions (Outside Japan)**
Cilostazol 100 mg 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 and erythromycin 500 mg tid after 7-day treatment with erythromycin 500 mg tid increased cilostazol C_{max} 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 C_{max} 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 hydrochloride 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.
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.
Coadministration of cilostazol 100 mg and omeprazole 40 mg qd after 7-day treatment with omeprazole 40 mg qd increased cilostazol C_{max} by 18% and AUC by 26% compared with administration of cilostazol alone.

PRECAUTIONS

1. **Careful Administration (Cilostazol should be administered with caution in the following patients.)**
(1) Patients on anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin, ticlopidine hydrochloride, or clopidogrel sulfate), thrombolytic drugs (e.g., urokinase or alteplase), or prostaglandin E_1 or its derivatives (e.g., alprostadil or limaprost alfadex) (See 8**. Drug Interactions.**)
(2) Patients during menstruation (There is a risk of menorrhagia.)
(3) Patients with bleeding tendency or predisposition to bleeding (If bleeding occurs, bleeding tendency may be increased.)
(4) Patients with coronary artery stenosis (Increased pulse rate possibly resulting from treatment with cilostazol could induce angina pectoris.) (See **WARNING**, item **(3)** under **2. Important Precautions**, and item **(1) Clinically significant adverse reactions, 1) Congestive heart failure, myocardial infarction, angina pectoris, and ventricular tachycardia** under 8**. Adverse Reactions**.)
(5) Patients with diabetes mellitus or abnormal glucose tolerance (Hemorrhagic adverse events may occur.)
(6) Patients with severe hepatic impairment (Blood concentration of cilostazol may be increased.) (See **PHARMACOKINETICS**.)
(7) Patients with renal impairment (Renal function may be aggravated. Blood concentrations of the metabolites of cilostazol may be increased.) (See item **7) Acute renal failure** under **(1) Clinically significant adverse reactions** in 7**. Adverse Reactions** and **PHARMACOKINETICS**.)
(8) Patients with hypertension with consistently high blood pressure (e.g., malignant hypertension) (See item **(2)** under 6**. Other Precautions.**)
(9) Patients with ventricular transposition, atrial transposition, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, multifocal ventricular ectopics and prolongation of the QTc interval.

2. **Important Precautions**
(1) Cilostazol should not be administered to patients with cerebral infarction until their condition has stabilized.
(2) When cilostazol is administered to patients with cerebral infarction, administration should be performed with caution for possible interaction with other drugs, such as antiplatelet drugs. In cerebral infarction patients with high blood pressure, blood pressure should be sufficiently controlled during cilostazol treatment. (See item **(1)** under **1. Careful Administration** and 8**. Drug Interactions**.)

(3) If an excessive increase in pulse rate is observed in patients with coronary artery stenosis during treatment with cilostazol, the dosage should be reduced or the drug discontinued and appropriate measures should be taken, since the increased pulse rate could induce angina pectoris. (See **WARNING**, item **(4)** under **1. Careful administration**, and item **(1) Clinically significant adverse reactions**, **1) Congestive heart failure, myocardial infarction, angina pectoris, and ventricular tachycardia** under **7. Adverse Reactions**.)

(4) Taking cilostazol with meal has been shown to increase the plasma concentrations of cilostazol, which may be associated with an increased incidence of adverse reactions. So, it's recommended to 3 hours interval between administration and meal. Especially, patients with high fat diet have to be careful, since a high fat meal following single-dosing of this drug 200 mg increase absorption, with an approximately 100% increase in Cmax and a 40% increase in AUC versus in fasting.

(5) Cilostazol is a drug with PDE3 inhibitory activity. Long-term comparative studies of cardiotonic agents with PDE3 inhibitory activity (milrinone[1)] and vesnarinone[2)]) in patients with congestive heart failure (NYHA class III to IV) conducted outside Japan demonstrated lower survival rates in patients receiving such cardiotonic agents compared with patients receiving placebo. In addition, prognosis following long-term treatment with PDE3 inhibitors, including cilostazol, has not yet been determined in patients without congestive heart failure.

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

(7) The effects of cilostazol on cerebral infarction have not been studied in patients with asymptomatic cerebral infarction.

3. Use in the Elderly

Elderly patients may be physiologically more sensitive to cilostazol than younger patients. It may be necessary to use a reduced dosage when prescribing cilostazol for elderly patients.

4. Use During Pregnancy, Delivery, or Lactation

(1) Cilostazol should not be used in women who are pregnant or who may possibly become pregnant. (Rat teratogenicity and peri- and post-natal studies of the drug showed an increased number of abnormal fetuses, low birth weight, and an increased number of stillborns.

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

5. Pediatric Use

The safe use of cilostazol in low birth weight infants, newborns, suckling infants, infants, and children has not been established. (Clinical experience in these populations is insufficient.)

6. Other Precautions

(1) 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.

(2) 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).

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

(4) Coadministration of a single dose of lovastatin 80 mg with a single dose of cilostazol 100 mg increased the lovastatin AUC by 64% compared with administration of lovastatin alone.

Warning

Patients should be closely monitored for any anginal symptoms (e.g., chest pain), since treatment with cilostazol may increase pulse rate, which could induce angina pectoris. [A significant increase in PRP (pressure rate product) was observed during long-term administration of cilostazol in a clinical trial to evaluate the drug's efficacy in the prevention of recurrence of cerebral infarction. Also, angina pectoris was observed in some of the patients treated with cilostazol.] **(See item (4) under 1. Careful Administration, item (3) under 2. Important Precautions, and item (1) Clinically significant adverse reactions, 1) Congestive heart failure, myocardial infarction, angina pectoris, and ventricular tachycardia under 7.Adverse Reactions.)**

7. Adverse Reactions

Treatment of ischemic symptoms, including ulceration, pain, and coldness of the extremities, in chronic arterial occlusion

<Clinical trials in Japan>

Of 1,035 patients included in safety evaluations, 90 patients (8.7%) had adverse drug reactions, including abnormal laboratory values. The most common adverse drug reactions were headache/dull headache (3.2%), tachycardia (1.0%), abdominal pain (0.8%), nausea/vomiting (0.8%), and dizziness (0.7%) (at time of approval of PLETAAL Tablets).

<Drug-use results surveys>

Of 3,335 patients included in safety evaluations, 209 patients (6.3%) had adverse drug reactions, including abnormal laboratory values. The most common adverse drug reactions

were headache/dull headache (3.4%), palpitation (0.7%), dizziness (0.5%), diarrhoea (0.3%), and nausea/vomiting (0.3%) (at time of completion of reexamination for PLETAAL Tablets).

Prevention of recurrence of cerebral infarction (excluding cardiogenic cerebral embolism)
<Clinical trials in Japan>
Of 520 patients included in safety evaluations, 137 patients (26.3%) had adverse drug reactions, including abnormal laboratory values. The most common adverse drug reactions were headache/dull headache (12.9%), palpitation (5.2%), nausea/vomiting (2.7%), dizziness (1.7%), and rash (1.3%) (at time of approval of additional indication for PLETAAL Tablets).
<Long-term special surveys>
Of 1,075 patients included in safety evaluations, 239 patients (22.2%) had adverse drug reactions, including abnormal laboratory values. The most common adverse drug reactions were headache/dull headache (4.6%), hepatic dysfunction (as indicated by elevated AST [GOT], ALT [GPT], Al-P, or LDH) (3.6%), palpitation (2.9%), tachycardia (2.2%), anemia (1.1%), and leukopenia (1.1%) (at time of completion of reexamination for PLETAAL Tablets).
<Post-marketing clinical trials>
Of 1,337 patients included in safety evaluations, 702 patients (52.5%) had adverse drug reactions, including abnormal laboratory values. The most common adverse drug reactions were headache/dull headache (17.7%), palpitation (10.5%), tachycardia (9.5%), arrhythmias (including atrial fibrillation, supraventricular tachycardia, supraventricular extrasystoles, and ventricular extrasystoles) (3.7%), and abdominal pain (3.0%) (at time of completion of reexamination for PLETAAL Tablets).

The incidences listed below under **Clinically significant adverse reactions** and **Other adverse reactions** are based on data reported at the time of initial approval and additional indication approval for cilostazol and from drug-use results surveys, long-term special surveys, and post-marketing clinical trials.
Adverse reactions reported after market launch for which the incidence could not be calculated are also included after the drug was placed on the market.

(1) Clinically significant adverse reactions

1) **Congestive heart failure**, **myocardial infarction, angina pectoris** (0.1% to less than 5% for each)**, and ventricular tachycardia** (incidence unknown*): 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 measures should be taken.
2) **Hemorrhage:**
<**Intracranial hemorrhage, such as cerebral hemorrhage** (0.1% to less than 5%) >
Intracranial hemorrhage, such as cerebral hemorrhage, (Early symptoms of intracranial hemorrhage include headache, nausea, vomiting, consciousness disturbance, and hemiplegia) may occur. If any such symptoms occur, the drug should be discontinued and appropriate measures should be taken.
<**Pulmonary hemorrhage** (less than 0.1%)**, hemorrhage in the digestive tract, epistaxis, and bleeding in the ocular fundus** (0.1% to less than 5% for each) >
Pulmonary hemorrhage, hemorrhage in the digestive tract, epistaxis, and bleeding in the ocular fundus may occur. If any such symptoms occur, the drug should be discontinued and appropriate measures should be taken.
3) **Gastric or duodenal ulcers** (0.1% to less than 5%): Gastric or duodenal ulcers with hemorrhage may occur. Patients should be closely monitored. If any signs of these adverse reactions are observed, the drug should be discontinued and appropriate measures should be taken.
4) **Pancytopenia, agranulocytosis** (both incidence unknown*)**, and thrombocytopenia** (0.1% to less than 5%): 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 measures should be taken.
5) **Interstitial pneumonia** (less than 0.1%): 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 measures, including adrenocorticotropic hormone administration, should be taken.
6) **Hepatic dysfunction** (0.1% to less than 5%) **and jaundice** (incidence unknown*): Hepatic dysfunction, 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 measures should be taken.
7) **Acute renal failure** (less than 0.1%): Acute renal failure may occur. Patients should be closely monitored, such as by renal function testing. If signs of renal failure are observed, the drug should be discontinued and appropriate measures should be taken.

*Information concerning incidence was not obtained because adverse reactions were voluntarily reported or occurred outside Japan.

(2) Other adverse reactions

Incidence Body System	More Than 5%	0.1% to Less Than 5%	Less Than 0.1%	Incidence Unknown*
Hypersensi-tivity[Note 1)]		Rash, eruption, and pruritus	Urticaria, etc.	Photosensi-tivity, and erythema
Cardio-vascular[Note 2)]		Palpitation, tachycardia, hot flushes, blood pressure increased, blood pressure decreased, arrhythmias (including atrial fibrillation, supraventricular tachycardia, supraventricular extrasystoles, and ventricular extrasystoles), etc.		
Psychoneuro-logical[Note 2)]	Headache /dull headache	Dizziness, insomnia, and numbness	Sleepiness, tremor, shoulder muscle stiffness, syncope/ transient loss of consciousness, etc.	
Gastro-intestinal		Abdominal pain, nausea, vomiting, anorexia, diarrhoea, heartburn, bloating, and dysgeusia	Thirst, etc.	
Hematological		Anaemia and leukopenia	Increased eosinophils, etc.	
Bleeding tendency		Subcutaneous haemorrhage, haematuria, etc.		
Hepatic		Increased AST (GOT), ALT (GPT), alkaline phosphatase, and LDH, etc.		
Renal		Increased blood urea nitrogen, creatinine, and uric acid, and pollakiuria	Urination impaired, etc.	
Other		Sweaty, oedema, chest pain, increased blood sugar, tinnitus, malaise, conjunctivitis, pyrexia, and alopecia	Pain, myalgia, and feeling of weakness	

Note 1: If such signs or symptoms are observed, the drug should be discontinued.

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

*Information concerning incidence was not obtained because Adverse reactions were voluntary reported or occurred outside Japan.

8. Drug Interactions

cilostazol is extensively metabolized by hepatic cytochrome P450 (CYP) enzymes, mainly CYP3A4 and, to a lesser extent, CYP2D6 and CYP2C19. (See **PHARMACOKINETICS**.)

Precautions for coadministration (Cilostazol should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Anticoagulants (e.g., warfarin) Antiplatelet drugs (e.g., aspirin, ticlopidine hydrochloride, and clopidogrel sulfate) Thrombolytic drugs (e.g., urokinase and alteplase) Prostaglandin E_1 or its derivatives (e.g., alprostadil and limaprost alfadex)	If bleeding occurs, bleeding tendency may be increased. Coagulation tests or other appropriate monitoring procedures should be employed when cilostazol is used in combination with these drugs in order to minimize the risk of adverse reactions such as hemorrhage.	Since cilostazol has an inhibitory effect on platelet aggregation, coadministration with these drugs may increase bleeding tendency.
Inhibitors of the drug metabolizing enzyme CYP3A4: Macrolide antibiotics (e.g., erythromycin), HIV protease inhibitors (e.g., ritonavir), azole antimycotics (e.g., itraconazole and miconazole), cimetidine, diltiazem hydrochloride, and grapefruit juice	The effects of cilostazol may be potentiated when it is used in combination with these drugs. cilostazol 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 cilostazol.	Blood concentrations of cilostazol are increased when cilostazol is coadministered with drugs or grapefruit juice components that inhibit the drug metabolizing enzyme CYP3A4.
Inhibitors of the drug metabolizing enzyme CYP2C19 (e.g., omeprazole)	The effects of cilostazol may be potentiated when it is used in combination with these drugs. Cilostazol should be reduced in dosage or started at a lower dose when coadministered with these drugs.	Blood concentrations of cilostazol are increased when cilostazol is coadministered with drugs that inhibit the drug metabolizing enzyme CYP2C19.

PHYSICOCHEMISTRY

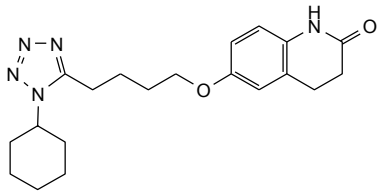
Non-proprietary name:

Cilostazol (JAN)

Chemical name:

6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butyloxy]-3,4-dihydroquinolin-2(1*H*)-one

Structural formula:



Molecular formula:

$C_{20}H_{27}N_5O_2$

Molecular weight:

369.46

Melting point:

158-162°C

Description:

Cilostazol occurs as white to pale yellowish white, crystals or crystalline powder. It is slightly soluble in methanol, in ethanol (99.5) and in acetonitrile, and practically insoluble in water.

STORAGE

PLETAAL® Tablets 50 & 100: **Store below 30°C**

PLETAAL® SR Capsules 100 mg: **Store below 30°C**

PACKAGING

PLETAAL® Tablets 50:

Boxes of 10 Blister of 10 Tablets

Reg. No.:DKL0318706110A1

PLETAAL® Tablets 100:

Boxes of 3 Blister of 10 Tablets

Reg. No.:DKL0318706110B1

PLETAAL® SR Capsules 100 mg

Boxes of 3 Blister of 10 Capsules

Reg. No: DKI1509700503A1

HARUS DENGAN RESEP DOKTER

PLETAAL® Tablets 50 &
PLETAAL® Tablets100

Manufactured by:
PT Otsuka Indonesia
Jl Sumber Waras No 25
Lawang, Malang 65216,Indonesia

Under license of:
Otsuka Pharmaceutical Co., Ltd.
2-9 Kanda-Tsukasamachi, Chiyoda-ku
Tokyo, Japan

PLETAAL SR Capsules 100 mg

Manufactured by:
Korea Otsuka Pharmaceutical Co., Ltd.
27, Jeyakgongdan 3-gil, Hyangnam-eup,
Hwaseong-si, Gyeonggi-do, 18622,
Korea.

Imported and Repacked by:
PT Otsuka Indonesia
Jl. Sumber Waras No 25
Lawang, Malang 65216, Indonesia

Under Auhorization of:
Otsuka Pharmaceutical Co., Ltd.
2-9 Kanda-Tsukasamachi, Chiyoda-ku
Tokyo, Japan

INFORMASI PRODUK UNTUK PASIEN
PLETAAL® Tablet 50
PLETAAL® Tablet 100
PLETAAL® SR Kapsul 100 mg
Cilostazol

Nama Obat : **PLETAAL®**

Bentuk sediaan : Tablet 50 & 100,
SR Kapsul 100 mg

Pemerian Obat : PLETAAL® Tablets 50: berwarna putih dengan emboss OG31 pada salah satu sisi.
PLETAAL® Tablet 100: berwarna putih dengan emboss OG30 pada salah satu sisi.
PLETAAL® SR Capsule: kapsul berwarna putih dengan print OG29 warna hitam yang berisi granul putih .

Komposisi obat : PLETAAL® Tablets 50 mengandung Cilostazol 50 mg
PLETAAL® Tablets 100 mengandung Cilostazol 100 mg
PLETAAL® SR Capsule 100 mg mengandung Cilostazol 100 mg

Apa yang terkandung dalam PLETAAL® ?
Zat aktif adalah Cilostazol

Zat tambahan :
PLETAAL® TABLET 50
PLETAAL® TABLET 100
Carmellose Calcium
Magnesium Stearate
Microcrystalline Cellulose
Hypromellose
Corn Starch
Purified Water

PLETAAL® SR
Microcrystalline Cellulose
Polysorbate 80
Corn Starch
Hydrated Silicon Dioxide
Pregelatinized Starch
Citric Acid Anhydrate
Hypromellose Capsule
Methacrylic Acid–Methyl Methacrylate Copolymer
Purified Water

Apa itu Cilostazol (PLETAAL®) ?

PLETAAL® termasuk golongan obat inhibitor phosphodiesterase type 3. Golongan ini memiliki mekanisme kerja antara lain melebarkan beberapa pembuluh darah dan menurunkan aktifitas penggumpalan pada sel darah yaitu trombosit/platelet di dalam pembuluh darah.

Anda mendapatkan resep PLETAAL® untuk pengobatan pada gejala iskemik, termasuk ulserasi, nyeri, rasa dingin pada ekstremitas, pada oklusi arteri yang kronis dan pencegahan dari kambuhnya infark serebral (tidak termasuk emboli otak kardiogenik)

Bagaimana seharusnya saya mengonsumsi PLETAAL®?

- Selalu gunakan PLETAAL® dengan tepat sesuai anjuran dokter. Anda harus bertanya kepada dokter atau apoteker jika Anda tidak yakin.
- Dosis yang umum digunakan pada PLETAAL® tablet adalah 100 mg Cilostazol dua kali sehari.
- Dosis yang umum digunakan pada Kapsul PLETAAL® SR adalah 200 mg Cilostazol, sekali sehari per oral. Kapsul PLETAAL® SR harus dimakan pada saat perut kosong .

Kadang-kadang Anda akan merasakan manfaat penggunaan PLETAAL® setelah 4-12 minggu pengobatan, sementara orang lain mungkin mengalami manfaat penggunaan setelah 16-24 minggu pengobatan.

PLETAAL® tidak cocok untuk anak-anak.

Jika Anda mengonsumsi PLETAAL® lebih dari yang dianjurkan.
Jika untuk alasan apapun Anda mengonsumsi **PLETAAL®** tablet atau kapsul lebih dari yang dianjurkan, Anda mungkin akan mengalami tanda-tanda atau gejala seperti sakit kepala hebat, diare, tekanan darah turun dan denyut jantung yang tidak teratur.

Jika Anda telah mengonsumsi tablet atau kapsul lebih dari dosis yang dianjurkan, segera hubungi dokter atau rumah sakit terdekat. Ingatlah untuk membawa kemasan PLETAAL® sehingga dapat dipastikan obat yang telah Anda gunakan.

Jika Anda lupa mengonsumsi PLETAAL®
Apabila Anda lupa mengonsumsi obat, jangan khawatir, tunggu sampai dosis berikutnya untuk mengonsumsi tablet atau kapsul selanjutnya dan kemudian teruskan sebagaimana dosis biasanya. JANGAN mengonsumsi dosis dua kali lipat untuk mencukupi tablet atau kapsul yang terlupakan.

Jika Anda berhenti mengonsumsi PLETAAL®
Jika Anda berhenti mengonsumsi **PLETAAL®** , nyeri pada kaki Anda mungkin akan kembali atau bahkan lebih parah. Oleh karena itu, sebaiknya Anda berhenti mengonsumsi **PLETAAL®** hanya jika Anda merasa bahwa efek samping yang ditimbulkan membutuhkan perhatian medis yang mendesak atau jika dokter Anda menganjurkan Anda untuk berhenti.

Sebelum Anda mengonsumsi PLETAAL®
JANGAN mengonsumsi PLETAAL®
- Apabila Anda memiliki alergi (hipersensitif) dengan cilostazol atau kandungan apapun dalam PLETAAL® tablet atau kapsul.
- Apabila Anda dalam kondisi gagal jantung.
- Apabila saat ini atau sebelumnya Anda pernah pingsan karena penyakit jantung, atau gangguan parah apapun pada denyut jantung.
- Apabila Anda mengetahui bahwa Anda dalam kondisi dimana dapat meningkatkan resiko pendarahan atau dapat menimbulkan luka memar, seperti: ulkus lambung yang aktif ,

serangan stroke enam bulan yang lalu, masalah dengan mata Anda yang disebabkan karena diabetes, apabila tekanan darah Anda tidak terkontrol dengan baik.
- Apabila Anda memiliki penyakit ginjal parah atau sedang dan atau penyakit hati yang serius.
- Apabila Anda hamil.

Perhatian khusus pada penggunaan PLETAAL®
Sebelum mengonsumsi PLETAAL® pastikan dokter Anda mengetahui:
- Apabila Anda memiliki masalah jantung yang berat atau masalah apapun dengan irama jantung Anda.
- Apabila Anda memiliki masalah dengan tekanan darah.

Apabila Anda perlu melakukan pembedahan termasuk pencabutan gigi, sampaikan kepada dokter atau dokter gigi Anda bahwa Anda sedang mengonsumsi PLETAAL®. Apabila Anda memiliki pengalaman mudah terjadi memar atau pendarahan, hentikan penggunaan PLETAAL® dan konsultasikan kepada dokter Anda

Penggunaan obat lain
Sebelum Anda memulai penggunaan PLETAAL®, sampaikan kepada dokter atau apoteker Anda apabila Anda sedang atau akhir-akhir ini mengonsumsi obat lain, termasuk obat tanpa resep.

Anda harus menginformasikan secara lengkap kepada dokter Anda apabila Anda mengonsumsi beberapa obat yang biasa digunakan untuk mengurangi rasa nyeri dan atau peradangan otot dan tulang sendi, atau apabila Anda mengonsumsi obat untuk mengurangi penggumpalan darah (misalnya aspirin (asam asetil salisilat), clopidogrel, warfarin, ticlopidine hydrochloride, obat-obatan trombolisis: urokinase, alteplase, alprostadil, limaprost alfadex). Apabila Anda sedang mengonsumsi pengobatan dengan PLETAAL®, dokter Anda dapat melakukan beberapa test darah rutin.

Obat-obat tertentu dapat mempengaruhi efek PLETAAL® ketika digunakan secara bersamaan.
Obat-obat tersebut dapat meningkatkan efek samping PLETAAL® atau membuat PLETAAL® kurang efektif. Demikian juga sebaliknya, apabila PLETAAL® diberikan bersama dengan obat lainnya.

Sebelum Anda mulai mengonsumsi PLETAAL® beritahukan kepada dokter Anda apabila Anda sedang mengonsumsi :
- Erythromycin (antibiotika golongan makrolida)
- Ritonavir (inhibitor Protease HIV)
- Itraconazole (antimikotik), miconazole (antimikotik)
- Cimetidine
- *Grapefruit Juice*
- Omeprazole
- Diltiazem

Jika Anda tidak yakin penggunaan PLETAAL® bersamaan dengan obat lain yang sedang Anda digunakan , tanyakan pada dokter atau apoteker Anda.

Sebelum Anda mengonsumsi PLETAAL®, informasikan kepada dokter Anda apabila Anda sedang mengonsumsi obat untuk tekanan darah tinggi, karena PLETAAL® memiliki tambahan efek penurunan pada tekanan darah Anda. Apabila tekanan darah Anda menurun terlalu rendah, ini dapat menyebabkan percepatan denyut jantung.

Anda masih tetap boleh mengonsumsi obat-obatan yang disebutkan diatas dan PLETAAL® secara bersamaan dan tentunya dokter Anda akan dapat memutuskan apa yang sesuai untuk Anda.

Mengonsumsi PLETAAL® bersama dengan makanan dan minuman
- PLETAAL® Tablet digunakan dua kali sehari pada saat sarapan pagi dan makan malam

- PLETAAL® SR kapsul harus digunakan satu kali sehari pada keadaan perut kosong tanpa adanya makanan.
- Selalu mengonsumsi air putih saat mengonsumsi PLETAAL® Tablet / Kapsul SR.

Apakah Cilostazol (PLETAAL®) dapat digunakan untuk wanita hamil dan menyusui ?

Wanita hamil tidak diperbolehkan mengonsumsi obat ini.
Wanita menyusui harus menghentikan menyusui selama mengonsumsi PLETAAL®

Apakah diperbolehkan untuk mengoperasikan mesin dan mengendarai mobil selama mengonsumsi Cilostazol (PLETAAL®) ?

PLETAAL® dapat menyebabkan rasa pusing. Apabila Anda merasa pusing setelah mengonsumsi PLETAAL®, jangan mengemudi dan menggunakan alat-alat atau mesin apapun serta informasikan kepada dokter atau apoteker Anda.

Efek apa saja yang mungkin terjadi bila mengonsumsi Cilostazol (PLETAAL®)?

Seperti semua obat-obat lainnya, PLETAAL® dapat menyebabkan efek samping, meskipun tidak setiap orang mengalaminya.

Apabila mengalami efek samping tersebut dibawah ini, Anda memerlukan perhatian medis dengan segera. Hentikan mengonsumsi PLETAAL® dan hubungi dokter atau segera pergi kerumah sakit terdekat.
• Serangan stroke
• Serangan jantung
• Gangguan jantung dimana dapat menyebabkan nafas pendek atau bengkak pada pergelangan kaki.
• Denyut jantung yang tidak beraturan (baru terjadi atau perburukan)
• Pendarahan yang terlihat
• Mudah memar
• Penyakit serius dengan pelepuhan pada kulit, mulut, mata dan alat kelamin.
• Warna kekuningan pada kulit atau pada bagian putih mata yang disebabkan dari gangguan hati atau gangguan darah (*jaundice* /penyakit kuning).

Anda juga harus mengatakan kepada dokter Anda segera apabila Anda mengalami demam atau sakit tenggorokan. Anda memerlukan pemeriksaan darah dan dokter Anda akan memutuskan pengobatan selanjutnya untuk Anda.

Efek samping dibawah ini telah dilaporkan pada penggunaan PLETAAL®. Anda harus mengatakan kepada dokter Anda secepat mungkin:

Efek samping yang sangat umum terjadi (mempengaruhi lebih dari 1 dari 10 orang)
• Sakit kepala
• Tinja abnormal
• Diare

Efek samping yang umum terjadi (mempengaruhi kurang dari 1 dari 10 orang, tetapi lebih dari 1 dari 100 orang)
• Denyut jantung cepat
• Palpitasi
• Nyeri dada
• Pusing
• Sakit tenggorokan
• Rhinitis (hidung berair)
• Nyeri perut

• Perasaan tidak nyaman pada perut (gangguan pencernaan)
• Perasaan sakit (mual atau muntah)
• Sendawa yang berlebihan (Buang angin)
• Pembengkakan pada pergelangan kaki, telapak kaki atau wajah.
• Ruam atau ada perubahan pada gambaran permukaan kulit.
• Gatal pada kulit
• Pendarahan di bawah kulit
• Lemas

Efek samping yang tidak umum terjadi (mempengaruhi kurang dari 1 dari 100 orang, tetapi lebih dari 1 dari 1.000 orang)
• Gangguan dengan aliran darah ke jantung.
• Napas pendek
• Pneumonia
• Batuk
• Menggigil
• Pendarahan yang tidak diinginkan
• Kecenderungan untuk mengeluarkan darah (di perut, mata, atau otot, mimisan dan darah dalam air ludah dan air seni).
• Penurunan jumlah sel darah merah di dalam darah.
• Pusing pada saat berdiri
• Pingsan
• Cemas
• Sulit tidur
• Mimpi yang tidak biasa
• Reaksi alergi
• Sakit dan nyeri
• Diabetes dan peningkatan kadar gula darah.
• Sakit perut (*gastritis*)

Dapat terjadi risiko yang tinggi dari pendarahan di mata pada penderita diabetes

Efek samping yang jarang terjadi (mempengaruhi kurang dari 1 dari 1000, tetapi lebih dari 1 dari 10.000 orang)
• Kecenderungan mengeluarkan darah untuk waktu yang lebih lama daripada biasanya.
• Peningkatan jumlah trombosit dalam darah
• Gangguan pada ginjal.

Efek samping-efek samping dibawah ini telah dilaporkan selama penggunaan PLETAAL namun tidak diketahui berapa sering efek samping ini terjadi:
• Perubahan pada tekanan darah
• Penurunan jumlah sel darah merah, sel darah putih dan trombosit di dalam darah
• Sulit bernapas
• Kesulitan dalam bergerak
• Demam
• Perasaan panas
• Eksim dan ruam kulit lainnya.
• Pengurangan rasa pada kulit
• Mata berair dan lengket (radang konjungtiva)
• Telinga berdengung (*tinnitus*)
• Tidak selera makan (*anorexia*)
• Gangguan hati termasuk radang hati (*hepatitis*)
• Perubahan pada air seni

Apabila efek samping apapun menjadi serius, atau apabila Anda menemui efek samping yang tidak terdapat pada brosur ini, sampaikan kepada dokter atau apoteker Anda.

Bagaimana cara menyimpan Cilostazol (PLETAAL®) ?

Simpan PLETAAL® jauh dari pandangan dan jangkauan anak-anak .

Tidak mengonsumsi PLETAAL® yang sudah kadaluarsa sebagaimana tercantum pada dus dan strip (pada PLETAAL® Tablet & PLETAAL® SR kapsul) dan pada dus. Tanggal kadaluarsa adalah tanggal terakhir dari bulan tersebut.

PLETAAL® Tablet 50 & 100 , disimpan dibawah temperatur 30 °C
PLETAAL® SR kapsul 100 mg disimpan dibawah temperatur 30 °C

PLETAAL® Tablet 50:
Dus, 10 blister @ 10 tablet No Reg : DKL0318706110A1

PLETAAL® Tablet 100:
Dus, 3 blister @ 10 tablet No Reg : DKL0318706110B1

PLETAAL® SR Kapsul 100 mg
Dus, 3 blister @ 10 kapsul No Reg : DKI1509700503A1

PLETAAL Tablet 50 &
PLETAAL Tablet 100

Diproduksi oleh :
PT Otsuka Indonesia
Jl Sumber Waras No 25
Lawang, Malang 65216, Indonesia

Di bawah lisensi dari:
Otsuka Pharmaceutical Co., Ltd.
2-9 Kanda Tsukasamachi, Chiyoda-ku,
Tokyo, Jepang

PLETAAL SR kapsul 100 mg

Diproduksi oleh :
Korea Otsuka Pharmaceutical Co., Ltd
27, Jeyakgondan 3-gil, Hyangnam-eup,
Hwaseong-si,Gyeonggi-do, 18622, Korea

Diimpor dan dikemas oleh:
PT Otsuka Indonesia
Jl Sumber Waras No 25
Lawang, Malang 65216, Indonesia

Di bawah otorisasi dari:
Otsuka Pharmaceutical Co., Ltd.
2-9 Kanda Tsukasamachi, Chiyoda-ku, Tokyo
Jepang

Harus dengan resep dokter