Cilostazol

Pletaal®
50mg tablet / 100mg tablet

Antiplatelet

WARNING

Patients should be closely monitored for any anginal symptoms (e.g., chest pain), since treatment with cilostazol (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 cilostazol (Pletaal) in a clinical study 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 (Pletaal)] (See item (4) under **1. Careful Administration,** item (3) under **2. Important Precautions,** item **(1) Clinically significant adverse reactions, 1) Congestive heart failure, myocardial infarction, angina pectoris, and ventricular tachycardia** under **4.Adverse Reactions, and CLINICAL STUDIES.)**

CONTRAINDICATIONS [Cilostazol(Pletaal) 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 **(4)** 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 **6. Use during Pregnancy, Delivery or Lactation.)**

DESCRIPTION

1. Composition

Brand name	Active Ingredient	Inactive Ingredients
Pletaal Tablets 50 mg	Each tablet contains 50 mg of cilostazol.	Microcrystalline cellulose, corn starch, carmellose calcium, hypromellose, and magnesium stearate
Pletaal Tablets 100 mg	Each tablet contains 100 mg of cilostazol.	Microcrystalline cellulose, corn starch, carmellose calcium, hypromellose, and magnesium stearate

2. Product Description

Brand name	Description	Appearance	Diameter (mm)	Thickness (mm)	Weight (mg)	Code
PLETAAL Tablets 50mg	White compressed tablets	OG 31	7	2.5	Approx. 115	OG 31
PLETAAL Tablets 100mg	White compressed tablets	OG 30	8	3.0	Approx. 170	OG 30

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)

<Precautions>

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

DOSAGE AND ADMINISTRATION

The usual adult dose of cilostazol (Pletaal) is 100 mg of cilostazol, twice daily, by the oral route. The dosage may be adjusted according to the age of the patient and the severity of symptoms.

PRECAUTIONS

1. Careful Administration (This drug should be administered with caution in the following patients.)

(1) Patients on anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin or ticlopidine), thrombolytic drugs (e.g., urokinase or alteplase), or prostaglandin E_1 or its derivatives (e.g., alprostadil) (See 3. 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 (Pletaal) could induce angina pectoris.) (See WARNING, item (3) under 2. Important Precautions, item (1) Clinically significant adverse reactions, 1) Congestive heart failure, myocardial infarction, angina pectoris, and ventricular tachycardia under 4. Adverse Reactions, and CLINICAL STUDIES.)
(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 severe renal impairment (Blood concentrations of cilostazol and its metabolites may be increased.) (See PHARMACOKINETICS.)
(8) Patients of severe hypertension with consistently high blood pressure (e.g., malignant hypertension) (See item (2) under 9. Other Precautions.)

2. Important Precautions

(1) Cilostazol (Pletaal) should not be administered to patients with cerebral infarction until their condition has stabilized.
(2) When cilostazol (Pletaal) 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, the blood pressure should be sufficiently controlled during cilostazol (Pletaal) treatment. (See item (1) under 1. Careful Administration and 3. Drug Interactions)
(3) If an excessive increase in pulse rate is observed in patients with coronary artery stenosis during treatment with cilostazol (Pletaal), the dosage should be reduced or the drug discontinued and appropriate corrective measures should be taken, since the increased pulse rate could induce angina pectoris. (See WARNING, item (4) under 1. Careful administration, item (1) Clinically significant adverse reactions, 1) Congestive heart failure, myocardial infarction, angina pectoris, and ventricular tachycardia under 4. Adverse Reactions, and CLINICAL STUDIES.)
(4) Cilostazol (Pletaal) is a drug with PDE3 inhibitory activity. Long-term comparative studies of cardiotonic agents with PDE3 inhibitory activity (milrinone and vesnarinone) 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 (Pletaal), has not yet been determined in patients without congestive heart failure.
(5) Left ventricular outflow tract obstruction has been reported in patients with sigmoid shaped interventricular septum. Monitor patients for the development of a new systolic murmur or cardiac symptoms after starting cilostazol.

3. Drug Interactions

Cilostazol (Pletaal) 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 (Pletaal) should be administered with care when coadministered with the following drugs.)

Drug	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Anticoagulants (e.g., warfarin) Antiplatelet drugs (e.g., aspirin and ticlopidine) Thrombolytic drugs (e.g., urokinase and alteplase) Prostaglandin E_1 or its derivatives (e.g., alprostadil)	If bleeding occurs, bleeding tendency may be increased. Coagulation tests or other appropriate monitoring procedures should be employed when cilostazol (Pletaal) is used in combination with these drugs in order to minimize the risk of adverse reactions such as hemorrhage.	Since cilostazol (Pletaal) 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, and grapefruit juice	The effects of cilostazol (Pletaal) may be potentiated when it is used in combination with these drugs, cilostazol (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 cilostazol (Pletaal).	Blood concentrations of cilostazol are increased when cilostazol (Pletaal) 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)		Blood concentrations of cilostazol are increased when cilostazol (Pletaal) is coadministered with drugs that inhibit the drug metabolizing enzyme CYP2C19.

4. Adverse Reactions

Adverse reactions, including abnormal laboratory tests, were reported in 436 (8.92%) of a total of 4,890 patients receiving cilostazol (Pletaal). (Figures are total cases reported from the time of initial approval up to the completion of reexamination and approval of the additional indication of cilostazol (Pletaal) Tablets 50 and 100 mg.) The following adverse reactions include those reported without information concerning frequency of occurrence after the drug was placed on the market.

(1) Clinically significant adverse reactions

1) **Congestive heart failure, myocardial infarction, angina pectoris,[note)] and ventricular tachycardia (frequency 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 corrective measures should be taken.
2) **Bleeding tendency:**
<Intracranial hemorrhage, such as cerebral hemorrhage (frequency unknown*)>
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 corrective measures should be taken.
< Pulmonary hemorrhage (frequency unknown*), hemorrhage in the digestive tract, epistaxis, and bleeding in the ocular fundus (less than 0.1%) >
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 corrective measures should be taken.
3) **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 should be taken.
4) **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 adrenocorticotropic hormone administration, should be taken.
5) **Hepatic dysfunction (0.1% to less than 5%), and jaundice (frequency 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 corrective measures should be taken.

Note: In a clinical study to evaluate cilostazol (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.
*Information concerning frequency of occurrence was not obtained because adverse reactions were either voluntarily reported or occurred outside Japan.

(2) Other adverse reactions

Frequency Body System	0.1% to less than 5%	Less than 0.1%	Frequency Unknown*
Hypersensitivity[1)]	Rash	Eruption, urticaria, and pruritus	Photosensitivity
Cardiovascular[2)]	Palpitation**, tachycardia and hot flushes	Blood pressure increase	Arrhythmias, including atrial fibrillation, supraventricular tachycardia, supraventricular extrasystoles, and ventricular extrasystoles, and blood pressure decrease
Psychoneurological[2)]	Headache/dull headache**, dizziness, insomnia, and numbness	Sleepiness and tremor	
Gastrointestinal	Abdominal pain, nausea, vomiting, anorexia, diarrhea, heartburn, and abdominal distention	Dysgeusia	
Hematological		Anemia and leucopenia	Increased eosinophils
Bleeding tendency	Subcutaneous haemorrhage	Hematuria	
Hepatic	Increase in AST (GOT), ALT (GPT), alkaline phosphatase, and LDH		
Renal		Increase blood urea nitrogen, creatinine, and uric acid	
Other	Sweating, edema, and chest pain	Increase blood sugar, tinnitus, pain, malaise, weakness, conjunctivitis, increased micturition frequency, fever and alopecia	

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

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* Information concerning frequency of occurrence was not obtained because adverse reactions were voluntarily reported or occurred outside Japan.
** In a clinical study to evaluate cilostazol (Pletaal) efficacy in the prevention of recurrence of cerebral infarction, the incidences of "headache and dull headache" and "palpitations" were respectively 63/520 (12.1%) and 27/520 (5.2%).

5. Use in the Elderly

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

6. Use during Pregnancy, Delivery, or Lactation

(1) Cilostazol (Pletaal) 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.)

7. Pediatric Use

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

8. Precautions Concerning Use

Cilostazol (Pletaal) Tablets 50 mg and 100 mg
At time of dispensing: 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.)

9. 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 the efficacy of cilostazol (Pletaal) in the prevention of recurrence of cerebral infarction, diabetes mellitus occurred or was worsened in more patients in the cilostazol (Pletaal) 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 (Pletaal) 100 mg increased the lovastatin AUC by 64% compared with administration of lovastatin alone.

PHARMACOKINETICS

1. Plasma Concentrations

(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-compartment model was 2.2 hours in the β -phase and 18.0 hours in the α -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 AUCinf 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 cilostazol (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 cilostazol (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)

Cilostazol (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. 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

- Cilostazol (Pletaal) Tablets were studied in a total of 226 patients with chronic arterial occlusive disease in open and double-blind studies. Based on global assessment, for ischemic symptoms, including ulceration, pain, and coldness of the extremities, the drug was judged to be either effective or very effective in 66.1% (119/180) and slightly effective or better in 85.0% (153/180) of patients with peripheral circulatory insufficiency.
- Cilostazol (Pletaal) Tablets were studied in a total of 1,034 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 cilostazol (Pletaal) and placebo groups, respectively, (total duration of observation: 873.8 and 973.7 person-years; incidence of recurrence: 30 and 56, respectively). The estimated risk reduction per person-year for cilostazol (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 rate was estimated to be 0.92% in the cilostazol (Pletaal) group and 0.82% in the placebo group, showing no significant difference between the two groups. In this study, occurrence of angina pectoris was reported in more patients in the cilostazol (Pletaal) group (6/516) than in the placebo group (0/518).

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 A2 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 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. Effect on Vascular Cells

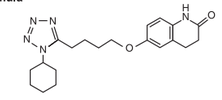
- Cilostazol suppressed ^{3}H-thymidine uptake in cultured human vascular smooth muscle cells.
- Cilostazol suppressed the depletion of lactate dehydrogenase from cultured human endothelial cells stimulated with homocysteine or lipopolysaccharide.

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)
Chemical name:
6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydroquinolin-2(1*H*)-one
Molecular formula
$C_{20}H_{27}N_5O_2$
Molecular weight
369.46
Structural formula



Melting point
158-162℃

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.

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

STORAGE AND HANDLING

Storage: Pletaal® tablets should be stored at temperature not exceeding 30℃

Expiration Date: Pletaal® tablets should be used before the expiration date indicated on the package

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

FAD Registration No.
Pletaal® 50-mg tablets DRP-6290
Pletaal® 100-mg tablets DRP-6289

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

REQUESTS FOR LITERATURE SHOULD BE ADDRESSED TO:

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