Drug Classification No.: 339

Regulatory Division : Prescription only

PLETAAL® Tablets 50 mg
PLETAAL® Tablets 100 mg
(cilostazol)

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ٹیبلٹس 50 ملی گرام اور 100 ملی گرام

[COMPOSITION]
Pletaal® Tablets 50mg
In 1 tablet of this drug,
*API:Cilostazol(JP).....50mg

*Other excipients: Microcrystalline cellulose, Magnesium stearate, Corn starch, Carboxymethylcellulose calcium, Hydroxypropylmethyl cellulose 2910

Pletaal® Tablets 100mg
In 1 tablet of this drug,
*API:Cilostazol(JP).....100mg

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[INDICATIONS]
1. Treatment of ischemic symptoms including ulceration, pain and coldness of the extremities, in chronic arterial occlusion (Buerger's disease, arteriosclerosis obliterans, diabetic peripheral angiopathy).
2. Prevention of recurrence of cerebral infarction (excluding cardiogenic cerebral embolism).

[DOSAGE & ADMINISTRATION]
The usual adult dose is 100mg of cilostazol, twice daily, by the oral route. The dosage may be adjusted according to the age of patients and the severity of symptoms.

[PRECAUTIONS]

1. 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 study to evaluate the drug's efficacy in the prevention of recurrence of cerebral infarction.] In clinical trials, angina pectoris was reported in patients treated with the drug.

2. This drug is contraindicated in the following patients.
(1) Patients with hemorrhage (e.g. hemophilia, increased capillary fragility, intracranial hemorrhage, upper gastrointestinal hemorrhage, hemorrhage in the urinary tract, hemoptysis, and hemorrhage in the vitreous body) and with any known predisposition to bleeding (e.g. active peptic ulceration, recent (within six months) haemorrhagic stroke, surgery within the previous three months, proliferative diabetic retinopathy, poorly controlled hypertension) (Bleeding tendency may be increased.)
(2) Patients with congestive heart failure. (Symptoms may be exacerbated.)
(3) Patients with a history of hypersensitivity to any ingredient of the drug
(4) Women who are pregnant or may possibly become pregnant or are nursing mothers (See 'Use during Pregnancy or Lactation' section.)

3. PRECAUTIONS
(1) This drug should be administered with caution in the following patients.
1) Patients on 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 and limaprost alfadex)
2) Patients during menstruation (There is a risk of menorrhagia.)
3) Patients with complication of coronary artery stenosis (Increased pulse rate possibly resulting from treatment with cilostazol could induce angina pectoris.)
4) Patients with severe renal failure (Creatine clearance ≤25 ml/min) (The blood concentration of cilostazol metabolite may be increased.) (See 'Others'.)
5) Patients with moderate or severe hepatic failure. (The blood concentration of cilostazol may be increased.) (See 'Others'.)
6) Patients with diabetes mellitus or abnormal glucose tolerance. (Hemorrhagic adverse events may occur.)
7) Patients of hypertension with consistently high blood pressure (e.g., malignant hypertension)
8) Patients with ventricular transposition, atrial transposition, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, multifocal ventricular ectopics and prolongation of the QTC interval
9) Patients with or having a risk of sigmoid shaped interventricular septum (especially elderly): 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.

4. ADVERSE REACTIONS
(1) Clinically significant adverse reactions
1) Bleeding tendency: Intracranial hemorrhage including cerebral hemorrhage (Initial symptom: headache, nausea and vomiting, disturbance of consciousness, hemiplegia.), pulmonary hemorrhage, occasionally subcutaneous hemorrhage, rarely gastrointestinal hemorrhage, nasal bleeding, bleeding of the ocular fundus and hematuria may occur. If any signs of bleeding are observed, the drug should be discontinued and appropriate corrective measures should be taken.
2) Blood: Pancytopenia, agranulocytosis, rarely thrombocytopenia, leucopenia, and aplastic anemia may occur. Patients should be closely monitored. If any signs are observed, the drug should be discontinued and appropriate corrective measures should be taken.
3) Interstitial pneumonia: Interstitial pneumonia accompanied by fever, cough, dyspnea, abnormal chest X-rays and eosinophilia may rarely 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.
4) Congestive heart failure, myocardial infarction, angina pectoris and tachycardia ventricular may occur. If any signs are observed, the drug should be discontinued and appropriate corrective measures should be taken.
5) Jaundice and occasionally the elevation of AST, ALT, ALP or LDH may occur. Patients should be closely monitored. If any signs are observed, the drug should be discontinued and appropriate corrective measures should be taken.

(2) Other adverse reactions
1) Hypersensitivity: Photosensitivity, occasionally rash, rarely eruption, urticaria and pruritus may occur. If any sign of this hypersensitivity is noted, the drug should be discontinued.
2) Body as a whole: Back pain, infection, chills, malaise, neck rigidity, pelvic pain, and retroperitoneal hemorrhage may occur.
3) Cardiovascular: Arrhythmia (including atrial fibrillation, atrial flutter, supraventricular tarchycardia, supraventricular extrasystoles and ventricular extrasystoles), decreased blood pressure, postural hypotension, occasionally palpitation, tachycardia, hot flushes and rarely increase in blood pressure may occur. In this case, appropriate corrective measure should be taken such as dosage reduction or discontinuation. Cerebral infarct, cerebral ischemia, heart arrest, myocardial ischemia, syncope, varicose vein and vasodilation were experienced in clinical trials, regardless of suspected drug relationship. Left ventricular outflow tract obstruction(Incidence Unknown※)
4) Psychoneurologic: Anxiety, neuralgia, inertia, abnormal dreams, occasionally headache• dull headache, dizziness, insomnia, numbness, rarely sleepiness, and tremor may occur. If such signs or symptoms are observed, appropriate corrective measures such as dosage reduction, discontinuation of this drug, should be taken.
5) Digestive: Abnormal stools, dyspepsia, cholelithiasis, colitis, duodenal ulcer, duodenitis, esophagitis, increase in γ-GTP, gastritis, gastroenteritis, gum hemorrhage, melena, peptic ulcer, periodontal abscess, gastric ulcer, tongue edema, occasionally abdominal pain, nausea, vomiting, anorexia, diarrhea, heartburn and abdominal distention may occur.
6) Hemic and Lymphatic: Polycythemia, purpura, increase in bleeding time, thrombothycemia, eosinophilia and rarely anemia may occur.
7) Metabolic & Nutritional: facial edema, peripheral edema, gout, hyperlipidemia and rare hyperglycaemia may occur.
8) Musculoskeletal: Myalgia, arthralgia, bone pain and bursitis may occur.
9) Respiratory: Increase in cough, pharyngitis, rhinitis, asthma, sinusitis and pneumonia may occur.
10) Endocrine: Diabetes mellitus may occur.
11) Skin and Appendages: Dry skin, furunculosis and skin hypertrophy may occur.
12) Sensory organ: Amblyopia, blindness, diplopia, ear pain, rarely tinnitus and conjunctivitis may occur.
13) Urogenital: Albuminuria, cystitis, vaginal hemorrhage, vaginitis and rarely urinary frequency may occur.
14) Renal: Renal failure, abnormal kidney function, an increase in BUN, creatinine and uric acid may rarely occur.
15) Others: Occasionally sweating, edema and chest pain, rarely pain, malaise and fever may rarely occur.

※ Information concerning incidence was not obtained because adverse reactions were voluntarily reported or occurred in foreign country.

(3) The result of Korean re-examination
38 adverse events (5.24%) in 34 patients were reported in the result of safety evaluation during post marketing surveillance which conducted in total 650 subjects regardless of causal relationship.
Adverse events which cannot be ruled out causal relationship with drug were 33 events (4.47%) in 29 subjects such as follows;
a. Central and peripheral nervous system disorders: headache 2.77% (18/650), anxiety(irritability) 0.15%(1/650)
b. Gastrointestinal disorders: diarrhea 0.46% (3/650), nausea 0.31% (2/650), dyspepsia 0.15% (1/650), vomiting 0.15% (1/650), anorexia 0.15% (1/650), abdominal pain 0.15% (1/650)
c. Skin and subcutaneous tissue disorders: pruritus 0.15% (1/650), rash 0.15% (1/650)
d. Psycho-neurologic disorders : somnolence 0.15% (1/650)
e. Heart rate abnormality : palpitation 0.15% (1/650)
Skeletal abnormality and sputum increase as additional unexpected adverse events which are not presented in previous label regardless of causal relationship were reported as 0.15% (1/649) respectively. And vomiting, skeletal abnormality and hemorrhage as serious adverse events regardless of causal relationship were reported as 0.15% (1/649) respectively.

(4) The following adverse events have been newly identified during analysis and evaluation of potential signal based on postmarketing adverse reports (1989-2015) in Korea. But, there was no causality assessment.
- Sensory system: hypoaesthesia

5. IMPORTANT PRECAUTIONS
(1) Cilostazol should not be administered to patients with cerebral infarction until their condition has stabilized.
(2) Attention should be paid to cerebral infarction patients who are receiving other anti-platelet agents, or to hypertension patients, whose blood pressure should be well- controlled during treatment.
(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 corrective measures taken, since the increased pulse rate could induce angina pectoris.
(4) Patients should be warned to report any other signs which might also suggest the early development of blood dyscrasia such as bleeding or easy bruising, pyrexia and sore throat whilst on therapy. A full blood count should be performed if infection is suspected or there is any other clinical evidence of blood dyscrasia. Cilostazol should be discontinued promptly if there is clinical or laboratory evidence of haematological abnormalities.
(5) Cilostazol may cause dizziness and patients should be warned to exercise caution before they drive or operate machinery.

6. DRUG INTERACTIONS
(1) Cilostazol is extensively metabolized by hepatic cytochrome P450 (CYP) enzymes, mainly CYP3A4 and, to a lesser extent, CYP2D6 and CYP2C19.
(2) 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 and limaprost alfadex) may cause a tendency to bleed, and frequent monitoring such as a blood coagulation test is required.

(3) Coadministration of CYP3A4 and CYP2C19 inhibitors (cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, itraconazole, miconazole, omeprazole, HIV-1 protease inhibitors, etc) may increase the blood concentration and potentiate the effects of cilostazol. Cilostazol should be reduced in dosage or started in a lower dose when coadministered with these drugs. Patients should be cautioned not to be drink grapefruit juice when receiving cilostazol.

(4) Coadministration of CYP3A4 and CYP2C19 substrates (cisapride, midazolam) may increase the blood concentration and potentiate the effects of cilostazol. Cilostazol should be reduced in dosage or started in a lower dose when coadministered with these drugs.

(5) Caution is needed when co-administering cilostazol with any other agent which has the potential to reduce blood pressure or vasodialators that cause reflex tachycardia (e.g. dihydropyridine calcium channel blockers) due to the possibility that there may be an additive hypotensive effect with a reflex tachycardia.

7. USE DURING PREGNANCY OR LACTATION

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

(2) Rat studies showed that cilostazol is distributed into breast milk in nursing rats. Nursing should be interrupted when the drug is administered to nursing women.

8. PEDIATRIC USE

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

9. GERIATRIC USE

Elderly patients may generally have lowered physical functions thus it may be necessary to reduce the dosage when prescribing this drug to elderly patients.

10. OVERDOSE

Information on acute overdose in humans is limited. The signs and symptoms can be anticipated to be severe headache, diarrhoea, hypotension, tachycardia and possibly cardiac arrhythmias. Patients should be 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 stomach should be emptied by induced vomiting or gastric lavage, as appropriate. The oral LD50 of cilostazol is >5.0 g/kg in mice and rats and >2.0g/kg in dogs.

11. OTHER PRECAUTIONS

(1) Cilostazol is a drug with PDE III inhibitory activity. Foreign long-term comparative studies conducted of cardiotonic agents with PDE III inhibitory activity in patients with congestive heart failure (NYHA class III to IV) 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.

(2) 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.

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

(4) 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).

(5) Coadministration of a single dose of a HMG-CoA reductase inhibitor, lovastatin 80mg with a single dose of cilostazol 100mg increased lovastatin AUC by 64% compared with administration of lovastatin alone.

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

(7) Taking cilostazol with food has been shown to increase the maximum plasma concentrations (Cmax) of cilostazol and it should be reduced in dosage, which may be associated with an increased incidence of adverse effects. Especially, patients with high fat diet have to be careful, since in case of high fat diet an absorption of this drug induce increase of 90% in Cmax and 25% in AUC.

(8) Pharmacokinetics in Patients with renal dysfunction: After 8-day administration of 100mg/day in patients with severe renal impairment, Cmax and AUC were 29% and 39% lower respectively than in subjects with normal renal function. The Cmax and AUC of an active metabolite were 173% and 209% greater in patients with severe renal impairment. There is no significant difference between in subjects with mild and moderate renal impairment and in normal subjects.

(9) Pharmacokinetics in Patients with hepatic dysfunction: There is no significant difference in patients with mild hepatic dysfunction and in normal subjects after single administration of 100mg (7% decrease in Cmax, 8% increase in AUC).

(10) Ketoconazole, Erythromycin, and Omeprazole: Coadministration of ketoconazole 400 mg increased cilostazol Cmax by 94% and AUC by 117%. Coadministration of erythromycin 500 mg increased cilostazol Cmax by 47% and AUC by 73%. Coadministration of a CYP2C19 inhibitor, Omeprazole increased the systemic exposure to a metabolite, 3,4-dehydro-cilostazol by 69%.

[STORAGE]

Store below 30°C.
Protect from sunlight and moisture.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only
Do not use after the expiration date indicated on the package.
PLETAAL is a prescription drug only

[SHELF-LIFE]

36 months after the date of manufacture

[PACKAGING UNIT]

Pletaal® Tablets 50mg
100 tablets (10 tablets/PTP x 10)
Pletaal® Tablets 100mg
100 tablets (10 tablets/PTP x 10)

احتیاطی تدابیر:

۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دُھوپ اور نمی سے بچائیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ میڈیکل پریکٹیشنر کے نسخے پر فروخت کریں۔

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