MOVIGRETAL

DOSAGE FORM
Tablets

COMPOSITION
Each tablet contains 100 mg of cilostazol.

INDICATIONS
- Treatment of ischemic symptoms; including ulceration, pain and coldness of the extremities in chronic arterial occlusion.
- Prevention of recurrence of cerebral infarction, including cardiogenic cerebral embolism.

DOSAGE & ADMINISTRATION
- The recommended dosage of Movigretal is 100 mg twice daily taken at least half an hour before or two hours after breakfast and dinner.
- A dose of 50 mg twice daily 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.

PHARMACOLOGY
Pharmacodynamic Properties
Cilostazol or 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone is a selective inhibitor of type-3 phosphodiesterase (PDE3) with therapeutic focus on increasing cAMP. An increase in cAMP results in an increase in the active form of protein kinase A (PKA), which is directly related with an inhibition in platelet aggregation. PKA also prevents the activation of an enzyme (myosin light-chain kinase) that is important in the contraction of smooth muscle cells, thereby exerting its vasodilatory effect, cilostazol’s antiaggregation effect in human platelets was augmented in the presence of vascular endothelial cells or prostaglandin E1.

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. Furthermore it inhibited thromboxane A2 production in activated human platelets. hereby inhibiting procoagulant activity of human platelets. In addition, cilostazol suppressed 3H-thymidine uptake in cultured human vascular smooth muscle cells, it also suppressed the depletion of lactate dehydrogenase from cultured human endothelial cells stimulated with homocysteine or lipopolysaccharide. 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 after being orally administered to patients with chronic arterial occlusion or cerebral infarction. The onset of cilostazol's platelet aggregation inhibitory effect was prompt in human 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). Cilostazol's antiaggregation effect in canine platelets was augmented in the presence of prostaglandin I\(_2\) or adenosine. Experiments in rabbits showed that cilostazol suppressed serotonin release from platelets without affecting serotonin and adenosine uptake by platelets, the drug also inhibited platelet aggregation induced by thromboxane A2.

**Pharmacokinetic Properties**

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 \(\alpha\)-phase and 18.0 hours the \(\beta\)-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 \(C_{\text{max}}\) and a 1.4-fold increase in AUC\(_{\text{inf}}\) compared with administration in a fasted state.

**Metabolism**

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

**Protein Binding**

- Cilostazol: > 95% (equilibrium dialysis in vitro, 0.1–6 \(\mu\)g/mL)
- Active metabolite OPC-13015: 97.4% (ultrafiltration in vitro, 1 \(\mu\)g/mL)
- Active metabolite OPC-13213: 53.7% (ultrafiltration in vitro, 1 \(\mu\)g/mL)

**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 (\(C_{\text{max}}\) by 29% and AUC by 39%) in plasma concentrations of cilostazol and marked increases (\(C_{\text{max}}\) 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.

**Hepatic Impairment (Outside Japan)**

Plasma concentrations of cilostazol following single oral administrations of cilostazol 100 mg in patients with mild to moderate hepatic impairment were similar (\(C_{\text{max}}\) decreased by 7%, AUC increased by 8%) to those in normal healthy individuals.
**PRODUCT INFORMATION**

**Elderly (≥ 65 years)**

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

**Drug Interactions**

- Cilostazol 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ by 94% and AUC by 129% compared with administration of cilostazol alone. (The oral formulation of the azole antymycotic ketoconazole has not yet been approved in Japan).
- Coadministration of diltiazem 180 mg with a single dose of cilostazol 100 mg increased cilostazol $C_{\text{max}}$ 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ by 18% and AUC by 26% compared with administration of cilostazol alone.

**CLINICAL STUDIES**

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

**SIDE EFFECTS**

- Adverse events were assessed in eight placebo-controlled clinical trials involving 2274 patients exposed to either 50 or 100 mg twice daily Cilostazol (n = 1301) or placebo (n = 973), with a median treatment duration of 127 days for patients on Cilostazol and 134 days for patients on placebo.
The only adverse event resulting in discontinuation of therapy in ≥ 3% of patients treated with cilostazol 50 or 100 mg twice daily was headache, which occurred with an incidence of 1.3%, 3.5%, and 0.3% in patients treated with Cilostazol 50 mg twice daily, 100 mg b.i.d, or placebo, respectively. Other frequent causes of discontinuation included palpitation and diarrhea, both 1.1% for cilostazol (all doses) versus 0.1% for placebo.

The most commonly reported adverse events, occurring in ≥ 2% of patients treated with Cilostazol 50 or 100 mg twice daily, are shown in the table (below).

Other events seen with an incidence of ≥ 2%, but occurring in the placebo group at least as frequently as in the 100 mg twice daily group were: asthenia, hypertension, vomiting, leg cramps, hyperesthesia, paresthesia, dyspnea, rash, hematuria, urinary tract infection, flu syndrome, angina pectoris, arthritis, and bronchitis.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Events</th>
<th>Cilostazol 50 mg twice daily (N = 303) %</th>
<th>Cilostazol 100 mg twice daily (N = 998) %</th>
<th>Placebo (N = 973) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td>Abdominal pain</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>27</td>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>14</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Palpitation</td>
<td>5</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Digestive</td>
<td>Abnormal stools</td>
<td>12</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>12</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Metabolic &amp; Nutritional</td>
<td>Peripheral edema</td>
<td>9</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Myalgia</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nervous</td>
<td>Dizziness</td>
<td>9</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Cough increased</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pharyngitis</td>
<td>7</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
<td>12</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

Less frequent adverse events (< 2%) that were experienced by patients exposed to cilostazol 50 mg twice daily or 100 mg twice daily in the eight controlled clinical trials and that occurred at a frequency in the 100 mg twice daily group greater than in the placebo group, regardless of suspected drug relationship, are listed below.
Body as a Whole

- Chills
- Face edema
- Fever
- Generalized edema
- Malaise
- Neck rigidity
- Pelvic pain
- Retroperitoneal hemorrhage

Cardiovascular

- Atrial fibrillation
- Atrial flutter
- Cerebral infarct
- Cerebral ischemia
- Congestive heart failure
- Cardiac arrest
- Hemorrhage
- Hypotension
- Myocardial infarction
- Myocardial ischemia
- Nodal arrhythmia
- Postural hypotension
- Supraventricular tachycardia
- Syncope
- Varicose vein
- Vasodilation
- Ventricular extrasystoles
- Ventricular tachycardia.

Digestive

- Anorexia
- Cholelithiasis
- Colitis
- Duodenal ulcer
- Duodenitis
- Esophageal hemorrhage
- Esophagitis
- Increased GGT
- Gastritis
- Gastroenteritis
- Gum hemorrhage
PRODUCT INFORMATION

- Hematemesis
- Melena
- Peptic ulcer
- Periodontal abscess
- Rectal hemorrhage
- Stomach ulcer
- Tongue edema

Endocrine
- Diabetes mellitus

Hemic & Lymphatic
- Anemia
- Ecchymosis
- Iron deficiency anemia
- Polycythemia
- Purpura

Metabolic & Nutritional
- Increased creatinine
- Gout
- Hyperlipemia
- Hyperuricemia

Musculoskeletal
- Arthralgia
- Bone pain
- Bursitis

Nervous
- Anxiety
- Insomnia
- Neuralgia

Respiratory
- Asthma
- Epistaxis
- Hemoptysis
- Pneumonia
- Sinusitis
Skin & Appendages
- Dry skin
- Furunculosis
- Skin hypertrophy
- Urticaria

Special Senses
- Amblyopia
- Blindness
- Conjunctivitis
- Diplopia
- Ear pain
- Eye hemorrhage
- Retinal hemorrhage
- Tinnitus

Urogenital
- Albuminuria
- Cystitis
- Urinary frequency
- Vaginal hemorrhage
- Vaginitis

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.
- Cilostazol is contraindicated in patients with congestive heart failure of any severity.

DRUG INTERACTIONS
- Cilostazol is extensively metabolized by hepatic cytochrome P450 (CYP) enzymes, mainly CYP3A4 and, to a lesser extent, CYP2D6 and CYP2C19.
- Since cilostazol has an inhibitory effect on platelet aggregation, coadministration with anticoagulants (e.g., warfarin) antiplatelet drugs (e.g., aspirin and ticlopidine) thrombolytic drugs (e.g., urokinase and alteplase) or prostaglandin E1, or its derivatives (e.g., alprostadil and limaprost alfadex) may increase bleeding tendency.
- Blood concentrations of cilostazol are increased when coadministered with CYP3A4 inhibitors; macrolide antibiotics (e.g., erythromycin), HIV protease inhibitors (e.g., ritonavir), azole antymycotics (e.g., Itraconazole and miconazole), cimetidine, diltiazem, and grapefruit juice.
Blood concentrations of cilostazol are increased when coadministered with CYP2C19 inhibitors such as omeprazole.

**PREGNANCY & LACTATION**

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

**PRECAUTIONS & WARNINGS**

- This drug should be administered with caution in the following cases:
  - Patients on anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin and ticlopidine), thrombolytic drugs (e.g., urokinase and alteplase), or prostaglandin E1, or its derivatives (e.g., alprostadil and limaprost alfadex).
  - Patients during menstruation, due to risk of menorrhagia
  - Patients with bleeding tendency or a predisposition to bleeding. If bleeding occurs, bleeding tendency may be increased.
  - Patients with coronary artery stenosis. Increased pulse rate possibly resulting from treatment with cilostazol could induce angina pectoris.
  - Patients with diabetes mellitus or abnormal glucose tolerance. Hemorrhagic adverse events may occur.
  - Patients with severe hepatic impairment, blood concentration of cilostazol may be increased.
  - Patients with severe renal impairment, blood concentrations of cilostazol and its metabolites may be increased.
  - Patients of severe hypertension with consistently high blood pressure (e.g., malignant hypertension)
- Cilostazol should **not** be administered to patients with cerebral infarction until their condition has stabilized.
- 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.
- 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 should be taken, since the increased pulse rate could induce angina pectoris.
- Cilostazol 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, has not yet been determined in patients without congestive heart failure.

- 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 clopidogrel, caution is advised for checking bleeding times during coadministration.

- 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.

PACKAGING

A carton box of 2 blisters, each containing 10 tablets each & an inner leaflet.

STORAGE

Store at temperatures not exceeding 30°C in a dry place.

Manufactured by the Nile Co. for Pharmaceuticals & Chemical Industries for Bioxell Pharma.