PLETAL®

(PLA-tal)

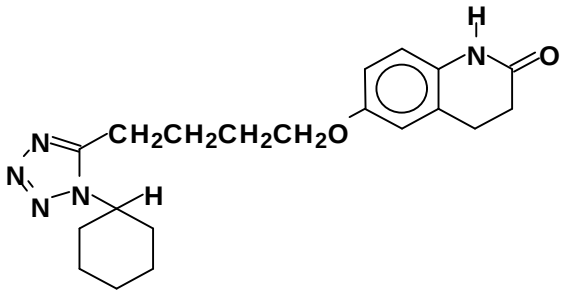
(cilostazol) (sil-OS-tah-zol)

Tablets

CONTRAINDICATION
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. PLETAL is contraindicated in patients with congestive heart failure of any severity.

DESCRIPTION

PLETAL (cilostazol) is a quinolinone derivative that inhibits cellular phosphodiesterase (more specific for phosphodiesterase III). The empirical formula of cilostazol is $C_{20}H_{27}N_5O_2$, and its molecular weight is 369.47. Cilostazol is 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone, CAS-73963-72-1. The structural formula is:



CILOSTAZOL

Cilostazol occurs as white to off-white crystals or as a crystalline powder that is slightly soluble in methanol and ethanol, and is practically insoluble in water, 0.1 N HCl, and 0.1 N NaOH.

PLETAL (cilostazol) tablets for oral administration are available in 50-mg triangular, and 100-mg round, white debossed tablets. Each tablet, in addition to the active ingredient, contains the following inactive ingredients: carboxymethylcellulose calcium, corn starch, hydroxypropyl methylcellulose 2910, magnesium stearate, and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism of the effects of PLETAL on the symptoms of intermittent claudication is not fully understood. PLETAL and several of its metabolites are cyclic AMP (cAMP) phosphodiesterase III inhibitors (PDE III inhibitors), inhibiting phosphodiesterase activity and suppressing cAMP degradation with a resultant increase in cAMP in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation.

PLETAL reversibly inhibits platelet aggregation induced by a variety of stimuli, including thrombin, ADP, collagen, arachidonic acid, epinephrine, and shear stress. Effects on circulating plasma lipids have been examined in patients taking PLETAL. After 12 weeks, as compared to placebo, PLETAL 100 mg b.i.d. produced a reduction in triglycerides of 29.3 mg/dL (15%) and an increase in HDL-cholesterol of 4.0 mg/dL (≅10%).

Cardiovascular Effects.

Cilostazol affects both vascular beds and cardiovascular function. It produces non-homogeneous dilation of vascular beds, with greater dilation in femoral beds than in

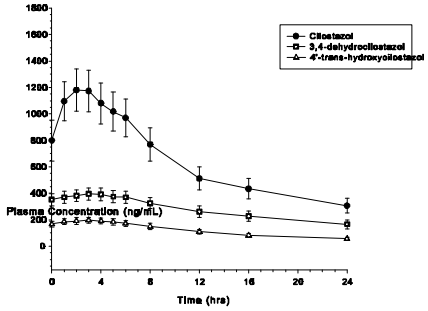
vertebral, carotid or superior mesenteric arteries. Renal arteries were not responsive to the effects of cilostazol.

In dogs or cynomolgous monkeys, cilostazol increased heart rate, myocardial contractile force, and coronary blood flow as well as ventricular automaticity, as would be expected for a PDE III inhibitor. Left ventricular contractility was increased at doses required to inhibit platelet aggregation. A-V conduction was accelerated. In humans, heart rate increased in a dose-proportional manner by a mean of 5.1 and 7.4 beats per minute in patients treated with 50 and 100 mg b.i.d., respectively. In 264 patients evaluated with Holter monitors, numerically more cilostazol-treated patients had increases in ventricular premature beats and non-sustained ventricular tachycardia events than did placebo-treated patients; the increases were not dose-related.

Pharmacokinetics:

PLETAL is absorbed after oral administration. A high fat meal increases absorption, with an approximately 90% increase in C_{max} and a 25% increase in AUC. Absolute bioavailability is not known. Cilostazol is extensively metabolized by hepatic cytochrome P-450 enzymes, mainly 3A4, with metabolites largely excreted in urine. Two metabolites are active, with one metabolite appearing to account for at least 50% of the pharmacologic (PDE III inhibition) activity after administration of PLETAL. Pharmaco-kinetics are approximately dose proportional. Cilostazol and its active metabolites have apparent elimination half-lives of about 11-13 hours. Cilostazol and its active metabolites accumulate about 2-fold with chronic administration and reach steady state blood levels within a few days. The pharmacokinetics of cilostazol and its two major active metabolites were similar in healthy normal subjects and patients with intermittent claudication due to peripheral arterial disease (PAD).

The mean ± SEM plasma concentration-time profile at steady state after multiple dosing of PLETAL 100 mg b.i.d. is shown below:



Distribution:

Plasma Protein and Erythrocyte Binding:

Cilostazol is 95-98% protein bound, predominantly to albumin. The mean percent binding for 3,4-dehydro-cilostazol is 97.4% and for 4´-trans-hydroxy-cilostazol is 66%. Mild hepatic impairment did not affect protein binding. The free fraction of cilostazol was 27% higher in subjects with renal impairment than in normal volunteers. The displacement of cilostazol from plasma proteins by erythromycin, quinidine, warfarin, and omeprazole was not clinically significant.

Metabolism and Excretion:

Cilostazol is eliminated predominately by metabolism and subsequent urinary excretion of metabolites. Based on *in vitro* studies, the primary isoenzymes involved in cilostazol's metabolism are CYP3A4 and, to a lesser extent, CYP2C19. The enzyme responsible for metabolism of 3,4-dehydro-cilostazol, the most active of the metabolites, is unknown.

Following oral administration of 100 mg radiolabeled cilostazol, 56% of the total analytes in plasma was cilostazol, 15% was 3,4-dehydro-cilostazol (4-7 times as active as cilostazol), and 4% was 4´-trans-hydroxy-cilostazol (one fifth as active as cilostazol). The primary route of elimination was the urine (74%), with the remainder excreted in the feces (20%). No measurable amount of unchanged cilostazol was excreted in the urine, and less than 2% of the dose was excreted as 3,4-dehydro-cilostazol. About 30% of the

dose was excreted in the urine as 4´-trans-hydroxy-cilostazol. The remainder was excreted as other metabolites, none of which exceeded 5%. There was no evidence of induction of hepatic microenzymes.

Special Populations:

Age and Gender:

The total and unbound oral clearances, adjusted for body weight, of cilostazol and its metabolites were not significantly different with respect to age and/or gender across a 50-to-80-year-old age range.

Smokers:

Population pharmacokinetic analysis suggests that smoking decreased cilostazol exposure by about 20%.

Hepatic Impairment:

The pharmacokinetics of cilostazol and its metabolites were similar in subjects with mild hepatic disease as compared to healthy subjects.

Patients with moderate or severe hepatic impairment have not been studied.

Renal Impairment:

The total pharmacologic activity of cilostazol and its metabolites was similar in subjects with mild to moderate renal impairment and in normal subjects. Severe renal impairment increases metabolite levels and alters protein binding of the parent and metabolites. The expected pharmacologic activity, however, based on plasma concentrations and relative PDE III inhibiting potency of parent drug and metabolites, appeared little changed. Patients on dialysis have not been studied, but, it is unlikely that cilostazol can be removed efficiently by dialysis because of its high protein binding (95-98%).

Pharmacokinetic and Pharmacodynamic Drug-Drug Interactions:

Cilostazol could have pharmacodynamic interactions with other inhibitors of platelet function and pharmacokinetic interactions because of effects of other drugs on its metabolism by CYP3A4 or CYP2C19. Cilostazol does not appear to inhibit CYP3A4

(see *Pharmacokinetic and Pharmacodynamic Drug-Drug Interactions*, Lovastatin).

Aspirin:

Short-term (≤4 days) coadministration of aspirin with PLETAL showed a 23-35% increase in inhibition of ADP-induced *ex vivo* platelet aggregation compared to aspirin alone; there was no clinically significant impact on PT, aPTT, or bleeding time compared to aspirin alone. There was no additive or synergistic effect on arachidonic acid-induced platelet aggregation. Effects of long-term coadministration in the general population are unknown. In eight randomized, placebo-controlled, double-blind clinical trials, aspirin was coadministered with cilostazol to 201 patients. The most frequent doses and mean durations of aspirin therapy were 75-81 mg daily for 137 days (107 patients) and 325 mg daily for 54 days (85 patients). There was no apparent greater incidence of hemorrhagic adverse effects in patients taking cilostazol and aspirin compared to patients taking placebo and equivalent doses of aspirin.

Warfarin:

The cytochrome P-450 isoenzymes involved in the metabolism of R-warfarin are CYP3A4, CYP1A2, and CYP2C19, and in the metabolism of S-warfarin, CYP2C9. Cilostazol did not inhibit either the metabolism or the pharmacologic effects (PT, aPTT, bleeding time, or platelet aggregation) of R- and S-warfarin after a single 25-mg dose of warfarin. The effect of concomitant multiple dosing of warfarin and PLETAL on the pharmacokinetics and pharmacodynamics of both drugs is unknown.

Omeprazole:

Coadministration of omeprazole did not significantly affect the metabolism of cilostazol, but the systemic exposure to 3,4-dehydro-cilostazol was increased by 69%, probably the result of omeprazole's potent inhibition of CYP2C19 (see DOSAGE AND ADMINISTRATION).

Erythromycin and other macrolide antibiotics:

Erythromycin is a moderately strong inhibitor of CYP3A4. Coadministration of erythromycin 500 mg q 8h with a single dose of cilostazol 100 mg increased cilostazol C_{max} by 47% and AUC by 73%. Inhibition of cilostazol metabolism by erythromycin

increased the AUC of 4´-trans-hydroxy-cilostazol by 141%. Other macrolide antibiotics would be expected to have similar effect (see DOSAGE AND ADMINISTRATION).

Diltiazem:

Diltiazem, a moderate inhibitor of CYP 3A4, has been shown to increase cilostazol plasma concentrations by approximately 53% (see DOSAGE AND ADMINISTRATION). This information was obtained from population pharmacokinetic analysis.

Quinidine:

Concomitant administration of quinidine with a single dose of cilostazol 100 mg did not alter cilostazol pharmacokinetics.

Strong Inhibitors of CYP3A4:

Strong inhibitors of CYP3A4, such as ketoconazole, itraconzaole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, and sertraline have not been studied in combination with cilostazol but would be expected to cause a greater increase in plasma levels of cilostazol and metabolites than erythromycin.

Lovastatin:

Coadministration of a single dose of lovastatin 80 mg with cilostazol at steady state did not result in clinically significant increases in lovastatin and its hydroxyacid metabolite plasma concentrations.

Clinical Efficacy

The ability of PLETAL to improve walking distance in patients with stable intermittent claudication was studied in eight large, randomized, placebo-controlled, double-blind trials of 12 to 24 weeks' duration using dosages of 50 mg b.i.d. (n=303), 100 mg b.i.d. (n=998), and placebo (n=973). Efficacy was determined primarily by the change in maximal walking distance from baseline (compared to change on placebo) on one of several standardized exercise treadmill tests.

Compared to patients treated with placebo, patients treated with PLETAL 50 or 100 mg

b.i.d. experienced statistically significant improvements in walking distances both for the distance before the onset of claudication pain and the distance before exercise-limiting symptoms supervened (maximal walking distance). The effect of PLETAL on walking distance was seen as early as the first on-therapy observation point of two or four weeks.

The following figure depicts the median and the mean percentage improvement in maximum walking distance, respectively, at study end for each of the eight studies.

Across the eight clinical trials, the range of improvement in maximal walking distance in patients treated with PLETAL 100 mg b.i.d., expressed as the percent mean and median change from baseline, was 28 to 100% and 17% to 72%, respectively. The corresponding changes in the placebo group were –10 to 30% and – 2 to 29%, respectively.

The Walking Improvement Questionnaire, which was administered in six of the eight clinical trials, assesses the impact of a therapeutic intervention on walking ability. In a pooled analysis of the six trials, patients treated with either PLETAL 100 mg b.i.d. or 50 mg b.i.d. reported improvements in their walking speed and walking distance as compared to placebo. Improvements in walking performance were seen in the various subpopulations evaluated, including those defined by gender, smoking status, diabetes mellitus, duration of peripheral artery disease, age, and concomitant use of beta blockers or of calcium channel blockers. PLETAL has not been studied in patients with rapidly progressing claudication or in patients with leg pain at rest, ischemic leg ulcers or

gangrene. Its long-term effects on limb preservation and hospitalization have not been evaluated. No reliable estimate of its effect on survival is available (see PRECAUTIONS).

INDICATIONS AND USAGE

PLETAL is indicated for the reduction of symptoms of intermittent claudication, as indicated by an increased walking distance.

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

PLETAL is contraindicated in patients with known or suspected hypersensitivity to any of its components.

PRECAUTIONS

PLETAL is contraindicated in patients with congestive heart failure. In patients without congestive heart failure, the long-term effects of PDE III inhibitors (including PLETAL) are unknown. Patients in the 3-6 month placebo-controlled trials of PLETAL were relatively stable (no recent myocardial infarction or strokes, no rest pain or other signs of rapidly progressing disease), and only 19 patients died (0.7% in the placebo group and 0.8% in the PLETAL group). The calculated relative risk of death of 1.2 has a wide 95% confidence limit (0.5-3.1). There are no data as to longer-term risk or risk in patients with more severe underlying heart disease.

Use with Clopidogrel.

There is no 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. Studies of concomitant use of cilostazol and clopidogrel are planned.

Information for Patients:

Please refer to the patient package insert.

Patients should be advised:

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

Hepatic Impairment:

Patients with moderate or severe hepatic impairment have not been studied in clinical trials.

Drug Interactions:

Since PLETAL is extensively metabolized by cytochrome P-450 isoenzymes, caution should be exercised when PLETAL is coadministered with inhibitors of CYP3A4 such as ketoconazole and erythromycin or inhibitors of CYP2C19 such as omeprazole. Pharmacokinetic studies have demonstrated that omeprazole and erythromycin significantly increased the systemic exposure of cilostazol and/or its major metabolites. Population pharmacokinetic studies showed higher concentrations of cilostazol among patients concurrently treated with diltiazem, an inhibitor of CYP3A4 (see CLINICAL PHARMACOLOGY, *Pharmacokinetic and Pharmacodynamic Drug-Drug Interactions*).

Pletal does not, however, appear to cause increased blood levels of drugs metabolized by CYP3A4, as it had no effect on lovastatin, a drug with metabolism very sensitive to CYP3A4 inhibition.

Cardiovascular Toxicity:

Repeated oral administration of cilostazol to dogs (30 or more mg/kg/day for 52 weeks, 150 or more mg/kg/day for 13 weeks, and 450 mg/kg/day for 2 weeks), produced cardiovascular lesions that included endocardial hemorrhage, hemosiderin deposition and fibrosis in the left ventricle, hemorrhage in the right atrial wall, hemorrhage and necrosis of the smooth muscle in the wall of the coronary artery, intimal thickening of the coronary artery, and coronary arteritis and periarteritis. At the lowest dose associated with cardiovascular lesions in the 52-week study, systemic exposure (AUC) to unbound cilostazol was less than that seen in humans at the maximum recommended human dose (MRHD) of 100 mg b.i.d. Similar lesions have been reported in the dog following the administration of other positive inotropic agents (including PDE III inhibitors) and/or vasodilating agents. No cardiovascular lesions were seen in rats following 5 or 13 weeks of administration of cilostazol at doses up to 1500 mg/kg/day. At this dose, systemic exposures (AUCs) to unbound cilostazol were only about 1.5 and 5 times (male and female rats, respectively) the exposure seen in humans at the MRHD. Cardiovascular lesions were also not seen in rats following 52 weeks of administration of cilostazol at doses up to 150 mg/kg/day. At this dose, systemic exposures (AUCs) to unbound cilostazol were about 0.5 and 5 times (male and female rats, respectively) the exposure in humans at the MRHD. (In female rats, cilostazol AUCs were similar at 150 and 1500 mg/kg/day). Cardiovascular lesions were also not observed in monkeys after oral administration of cilostazol for 13 weeks at doses up to 1800 mg/kg/day. While this dose of cilostazol produced pharmacologic effects in monkeys, plasma cilostazol levels were less than those seen in humans given the MRHD, and those seen in dogs given doses associated with cardiovascular lesions.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Dietary administration of cilostazol to male and female rats and mice for up to 104 weeks, at doses up to 500 mg/kg/day in rats and 1000 mg/kg/day in mice, revealed no evidence of carcinogenic potential. The maximum doses administered in both rat and mouse studies were, on a systemic exposure basis, less than the human exposure at the MRHD of the drug. Cilostazol tested negative in bacterial gene mutation, bacterial DNA repair, mammalian cell gene mutation, and mouse *in vivo* bone marrow chromosomal aberration assays. It was, however, associated with a significant increase in chromosomal aberrations in the *in vitro* Chinese Hamster Ovary Cell assay.

Cilostazol did not affect fertility or mating performance of male and female rats at doses as high as 1000 mg/kg/day. At this dose, systemic exposures (AUCs) to unbound cilostazol were less than 1.5 times in males, and about 5 times in females, the exposure in humans at the MRHD.

Pregnancy:

Pregnancy Category C: In a rat developmental toxicity study, oral administration of 1000 mg cilostazol/kg/day was associated with decreased fetal weights, and increased incidences of cardiovascular, renal, and skeletal anomalies (ventricular septal, aortic arch and subclavian artery abnormalities, renal pelvic dilation , 14^{th} rib and retarded ossification). At this dose, systemic exposure to unbound cilostazol in nonpregnant rats was about 5 times the exposure in humans given the MRHD. Increased incidences of ventricular septal defect and retarded ossification were also noted at 150 mg/kg/day (5 times the MRHD on systemic exposure basis). In a rabbit developmental toxicity study, an increased incidence of retardation of ossification of the sternum was seen at doses as low as 150 mg/kg/day. In nonpregnant rabbits given 150 mg/kg/day, exposure to unbound cilostazol was considerably lower than that seen in humans given the MRHD, and exposure to 3,4-dehydro-cilostazol was barely detectable.

When cilostazol was administered to rats during late pregnancy and lactation, an

increased incidence of stillborn and decreased birth weights of offspring was seen at doses of 150 mg/kg/day (5 times the MRHD on a systemic exposure basis).
There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers:
Transfer of cilostazol into milk has been re-ported in experimental animals (rats). Because of the potential risk to nursing infants, a decision should be made to discontinue nursing or to discontinue PLETAL.

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

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

ADVERSE REACTIONS
Adverse events were assessed in eight placebo- controlled clinical trials involving 2274 patients exposed to either 50 or 100 mg b.i.d. PLETAL (n=1301) or placebo (n=973), with a median treatment duration of 127 days for patients on PLETAL and 134 days for patients on placebo.

The only adverse event resulting in discontinuation of therapy in ≥3% of patients treated

with PLETAL 50 or 100 mg b.i.d. was headache, which occurred with an incidence of 1.3%, 3.5%, and 0.3% in patients treated with PLETAL 50 mg b.i.d., 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 PLETAL 50 or 100 mg b.i.d., are shown in the table (to the right).

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

Adverse Events (AEs) by Body System	**Most Commonly Reported AEs (Incidence ≥2%) in Patients on PLETAL (PLT) 50 mg b.i.d. or 100 mg b.i.d. and Occurring at a Rate in the 100 mg b.i.d. Group Higher Than in Patients on Placebo**		
	PLT 50 mg b.i.d. (N=303) %	PLT 100 mg b.i.d. (N=998) %	Placebo (N=973) %
BODY AS A WHOLE			
Abdominal pain	4	5	3
Back pain	6	7	6
Headache	27	34	14
Infection	14	10	8
CARDIOVASCULAR			
Palpitation	5	10	1
Tachycardia	4	4	1
DIGESTIVE			
Abnormal stools	12	15	4
Diarrhea	12	19	7
Dyspepsia	6	6	4
Flatulence	2	3	2
Nausea	6	7	6
METABOLIC & NUTRITIONAL			
Peripheral edema	9	7	4
MUSCULO-SKELETAL			
Myalgia	2	3	2
NERVOUS			
Dizziness	9	10	6
Vertigo	3	1	1
RESPIRATORY			
Cough increased	3	4	3
Pharyngitis	7	10	7
Rhinitis	12	7	5

Less frequent adverse events (<2%) that were experienced by patients exposed to PLETAL 50 mg b.i.d. or 100 mg b.i.d. in the eight controlled clinical trials and that occurred at a frequency in the 100 mg b.i.d. group greater than placebo, 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, heart 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, GGT increased, gastritis, gastroenteritis, gum hemorrhage, hematemesis, melena, peptic ulcer, periodontal abscess, rectal hemorrhage, stomach ulcer, tongue edema.

Endocrine: Diabetes mellitus.

Hemic and Lymphatic: Anemia, ecchymosis, iron deficiency anemia, polycythemia, purpura.

Metabolic and Nutritional: Creatinine increased, gout, hyperlipemia, hyperuricemia.

Musculoskeletal: Arthralgia, bone pain, bursitis.

Nervous: Anxiety, insomnia, neuralgia.

Respiratory: Asthma, epistaxis, hemoptysis, pneumonia, sinusitis.

Skin and 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.

OVERDOSAGE

Information on acute overdosage with PLETAL in humans is limited. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: severe headache, diarrhea, hypotension, tachycardia, and possibly cardiac arrhythmias. The patient should be carefully observed and given supportive treatment. Since cilostazol is highly protein-bound, it is unlikely that it can be efficiently removed by hemodialysis or peritoneal dialysis. The oral LD_{50} of cilostazol is >5.0 g/kg in mice and rats and >2.0 g/kg in dogs.

DOSAGE AND ADMINISTRATION

The recommended dosage of PLETAL is 100 mg b.i.d., taken at least half an hour before or two hours after breakfast and dinner. A dose of 50 mg b.i.d. should be considered during coadministration of such inhibitors of CYP3A4 as ketoconazole, itraconazole, erythromycin and diltiazem, and during coadministration of such inhibitors of CYP2C19 as omeprazole. CYP3A4 is also inhibited by grapefruit juice. Because the magnitude and timing of this interaction have not yet been investigated, patients receiving PLETAL should avoid consuming grapefruit juice.

Patients may respond as early as 2 to 4 weeks after the initiation of therapy, but treatment for up to 12 weeks may be needed before a beneficial effect is experienced.

Discontinuation of Therapy: The available data suggest that the dosage of PLETAL can be reduced or discontinued without rebound (i.e., platelet hyperaggregability).

HOW SUPPLIED

PLETAL is supplied as 50-mg and 100-mg tablets. The 50-mg tablets are white, triangular, debossed with PLETAL 50, and provided in bottles of 60 tablets (NDC #59148-003-16), and hospital unit dose packs of 100 tablets (NDC #59148-003-35). The 100-mg tablets are white, round, debossed with PLETAL 100, and provided in bottles of 60 tablets (NDC #59148-002-16), and hospital unit dose packs of 100 tablets (NDC #59148-002-35).

Rx ONLY.

STORAGE

Store PLETAL tablets at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

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