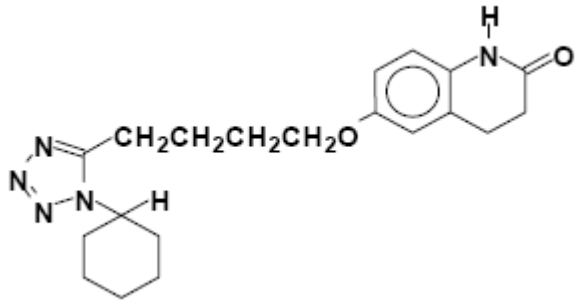
PRODUCT INFORMATION

PLETAL® (cilostazol)

NAME OF THE MEDICINE

Pletal (cilostazol) is a quinolinone derivative which inhibits cellular phosphodiesterase (more specific for phosphodiesterase 3).



Molecular formula	$C_{20}H_{27}N_5O_2$
Molecular wt	369.47
CAS	73963-72-1

The IUPAC name for cilostazol is 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone.

DESCRIPTION

Cilostazol is slightly soluble in methanol and ethanol and practically insoluble in water, 0.1N HCl, and 0.1N NaOH.

The tablets are an immediate release formulation containing maize starch, microcrystalline cellulose, carmellose calcium, hypromellose and magnesium stearate.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitor

Animal studies have shown Pletal to have vasodilator effects and this has been demonstrated in small studies in man where ankle blood flow was measured by strain gauge plethysmography. Pletal also inhibits smooth muscle cell proliferation in rat and human smooth muscle cells in vitro, and inhibits the release of platelet-derived growth factor and PF-4 from human platelets.

Studies in animals (in vivo and ex vivo) have shown that Pletal causes inhibition of platelet aggregation. The inhibition is effective against a range of aggregants (including shear stress, arachidonic acid, collagen, ADP and adrenaline); in man the inhibition lasts for up to 12 hours, and on cessation of administration of Pletal recovery of aggregation occurs within 48-96 hours, without rebound hyperaggregability.

Pharmacokinetics

Absorption: Following multiple doses of Pletal 100 mg twice daily in patients with peripheral vascular disease, steady state is achieved within 4 days. The Cmax of Pletal and its two active metabolites increase less than proportionally with increasing doses. However, the AUC for Pletal and its metabolites increase approximately proportionately with dose.

Compared to the fasted state, the mean C_{max} of Pletal is 16% higher when dosed 30 minutes prior to a meal and 93% higher when dosed 2 hours after a meal. AUC_{0-t} is similar to the fasted state when taken 30 minutes prior to a meal but administration 2 hours after a meal increases AUC_{0-t} 22%. $AUC_{0-\infty}$ is increased 5-7% when the dosing occurs 30 minutes prior to or 2 hours after a meal, compared to the fasting state.

Dosing within 10 minutes of a meal increases C_{max}, $AUC_{0-t,}$ $AUC_{0-\infty}$ by 86%, 21% and 19% respectively compared to the fasting state.

The absolute bioavailability of Pletal is not known.

Distribution: Pletal is 95-98% protein bound, predominantly to albumin. The dehydro metabolite and 4'-trans-hydroxy metabolite are 97.4% and 66% protein bound respectively.

Metabolism: Pletal is eliminated predominantly by metabolism and subsequent urinary excretion of metabolites. The primary isoenzymes involved in its metabolism are cytochrome P-450 CYP3A4, to a lesser extent, CYP2C19 and CYP2D6, and to an even lesser extent CYP1A2. There are two major metabolites, a dehydro-cilostazol and a 4'-trans-hydroxy cilostazol, both of which have similar apparent half-lives. The dehydro metabolite is about 4 times as active a platelet anti-aggregant as the parent compound and the 4'-trans-hydroxy metabolite is 0.3-0.4 times as active.

There is no evidence that Pletal induces hepatic microsomal enzymes following repeated oral administration to rats.

Elimination: The apparent elimination half-life of Pletal is 10.5 hours.

The primary route of elimination is urinary (74%) with the remainder excreted in the faeces. No measurable amount of unchanged Pletal is excreted in the urine, and less than 2% of the dose is excreted as the dehydro-cilostazol metabolite. Approximately 30% of the dose is excreted in the urine as the 4'-trans-hydroxy metabolite. The remainder is excreted as metabolites, none of which exceed 5% of the total excreted.

Elderly: The pharmacokinetics of Pletal and its metabolites were not significantly affected by age or gender in healthy subjects aged between 50-80 years.

Renal Insufficiency: In subjects with severe renal impairment, the free fraction of Pletal was 27% higher and both C_{max} and AUC were 29% and 39% lower respectively than in subjects with normal renal function. The C_{max} and AUC of the dehydro metabolite were 41% and 47% lower respectively in the severely renally impaired subjects compared to subjects with normal renal function. The C_{max} and AUC of 4'-trans-hydroxy cilostazol were 173% and 209% greater in subjects with severe renal impairment.

Hepatic Insufficiency: There are no data in patients with moderate to severe hepatic impairment although Pletal is extensively metabolised by hepatic enzymes.

CLINICAL TRIALS

Peripheral artery occlusive disease is commonly divided in the Fontaine stages or Rutherford categories. The Fontaine system consists of 4 stages: stage I identifies those patients who are asymptomatic, stages IIa and IIb represent those patients with mild and moderate-to-severe intermittent claudication. Patients with ischemic rest pain are categorized as stage III, and stage IV represents patients with disease that has advanced to ulcerations and gangrene. In the Rutherford system, there are 4 grades (0–III) that are further divided into 6 categories according to the severity of symptoms. In the Rutherford system, grade 0 represents patients with asymptomatic disease characterized by a normal treadmill test. Grade I includes individuals with intermittent claudication, subcategorized according to severity from mild to moderate to severe. Grade II/category 4 identifies patients experiencing ischemic rest pain. Grade III/categories 5 and 6 represent patients with either limited or extended ischemic lesions.

Classification of peripheral arterial disease: Fontaine´s stages and Rutherford´s categories

Fontaine		Rutherford		
Stage	**Clinical**	**Grade**	**Category**	**Clinical**
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischaemic rest pain	II	4	Ischaemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

Nine efficacy (8 Phase III and 1 Phase IV) and 1 safety (Phase IV long-term) double-blind, parallel-group trials were conducted. In the 9 efficacy trials a total of 3,482 patients were randomised. .All trials were multi-centre, double-blind, placebo-controlled, parallel-group trials and contained treatment groups of Pletal 100 mg bid and placebo. Patients recruited in these trials suffered from moderate to severe IC Fontaine Stage II (feeling pain when walking and with limited walking distance).

The patients enrolled in the efficacy trials were ≥ 40 years of age with symptomatic lower extremity PAD of ≥ 6 months in duration, and with no significant change in symptoms severity for a minimum of 3 months before enrolment. Claudication was defined uniformly in all trials as cramping, aching, fatigue, or any patient-reported pain in 1 or both legs that occurred during walking and was sufficient to cause the subject to reduce the pace or cease ambulation. The definition of PAD required Doppler measurement of an ABI ≤ 0.90 (8 trials) or ≤ 0.80 (1 trial). A decrease in post-exercise systolic ankle pressure of ≥ 10 mmHg was additional confirmatory evidence of PAD; patients lacking ABI criteria but who had a decrease of 20 mmHg were eligible for enrolment. Patients were not included if they had any of the following: Buerger's disease, pain at rest attributable to ischemia, ulceration, and gangrene, ischemic tissue necrosis, surgical or endovascular procedures within the past 3 months, unstable coronary artery disease or a coronary intervention within the past 6 months, deep vein thrombosis within the past 3 months, symptomatic cardiac arrhythmias or conditions other than claudication that limited exercise capacity.

Baseline characteristics of the nine randomised clinical trials (randomised patients, excluding 50 & 150 mg b.i.d. doses)

	Pletal 100mg BID	**Placebo**
Total number, n	1258	1233
Male, n (%)	951 (75.6)	941 (76.3)
Age, years (mean ± SD)	65.5 ± 9.3	65.8 ± 9.4
Age > 65 years (%)	57.5	57.7
Ethnicity (% Caucasian)	89.1	86.1
Weight, kg (mean ± SD)	80.3 ± 15.8	80.2 ± 15.4
PAD duration		
≥ 6 months to ≤ 5 years (%)	59.6	62.5
> 5 years (%)	40.1	37.4
Diabetes (%)	26.0	27.4
Hypertension (%)	62.9	63.1
Smoking status		
Never (%)	8.3	8.5
Prior (%)	50.5	52.1
Current (%)	41.3	39.4

From data generated in these nine placebo-controlled studies (where 1,135 efficacy patients excluding 50 mg & 150 mg b.i.d. groups were exposed to Pletal), it has been demonstrated that Pletal improves exercise capacity as judged by changes in Absolute Claudication Distance (ACD, or maximal walking distance) and Initial Claudication Distance (ICD**,** or pain-free walking distance) upon treadmill testing. Following 24 weeks treatment, Pletal 100 mg b.i.d. increases in ACD ranged from 60.4 -129 metres, whilst mean ICD increases ranged from 47.3 - 93.6 metres.

A meta-analysis based on weighted mean differences across the nine studies indicated that there was a significant absolute overall post-baseline improvement of 42 m in maximal walking distance (ACD) for Pletal 100 mg b.i.d. over the improvement seen under placebo. This effect appeared lower in diabetics than in non-diabetics.

Estimated Treatment Effect (95% CI) for Pletal (CLZ) 100 mg bid vs. Placebo (PLC) on Maximal Walking Distance (ACD)

Study No.	Duration (wks)	Number of Patients (Efficacy ITT)	Treatment & Dosage	Treatment Effect over Placebo (95% CI)	p-value
Pooled		2266	CLZ 100 mg bid PLC	1.15 (1.11 – 1.19)	< 0.001
21-92-202	24	140 140	CLZ 100 mg bid PLC	1.31 (1.17 – 1.47)	< 0.001
21-94-201	24	124 125	CLZ 100 mg bid PLC	1.21 (1.09 – 1.35)	< 0.0003
21-94-301	24	118 122	CLZ 100 mg bid PLC	1.06 (0.94 – 1.18)	< 0.3616
21-96-202	24	205 226	CLZ 100 mg bid PLC	1.15 (1.06 – 1.25)	< 0.0005
21-98-213	24	231 218	CLZ 100 mg bid PLC	1.03 (0.95 – 1.12)	< 0.4749
21-94-203	16	119 120	CLZ 100 mg bid PLC	1.29 (1.17 – 1.41)	< 0.0001
21-90-201	12	52 25	CLZ 100 mg bid PLC	1.41 (1.14 -1.74)	< 0.0016
21-93-201	12	86 89	CLZ 100 mg bid PLC	1.13 (1.01 – 1.26)	< 0.0347
21-95-201	12	60 66	CLZ 100 mg bid PLC	1.02 (0.88 – 1.18)	< 0.7925

Percent Mean Change Maximal Walking Distance (ACD) from Baseline to End of Treatment

Study No.	Duration (wks)	Number of Patients (Efficacy ITT)	Treatment & Dosage	Mean at Baseline (m)	Mean at Endpoint (m)	Individual % change (mean)	Group % mean change
Pooled		1135 1131	CLZ 100 mg bid. PLC	172.2 180.1	259.6 223.8	53.4 30.8	50.7 24.3
21-92-202	24	140 140	CLZ 100 mg bid. PLC	129.7 147.8	258.8 174.6	86.0 30.6	99.6 18.1
21-94-201	24	124 125	CLZ 100 mg bid PLC	117.3 120.9	195.6 141.2	56.2 20.8	66.7 16.8
21-94-301	24	118 122	CLZ 100 mg bid PLC	128.1 129.0	214.4 181.6	54.9 46.1	67.3 40.8
21-96-202	24	205 226	CLZ 100 mg bid. PLC	242.5 234.9	349.9 299.6	53.9 33.5	44.3 27.5
21-98-213	24	231 218	CLZ 100 mg bid PLC	136.5 140.3	196.9 199.3	43.6 41.4	44.2 42.1
21-94-203	16	119 120	CLZ 100 mg bid PLC	236.3 249.7	332.6 281.1	47.4 12.9	40.8 12.6
21-90-201	16	52 25	CLZ 100 mg bid PLC	141.9 168.6	231.7 152.1	59.6 2.7	63.3 -9.8
21-93-201	12	86 89	CLZ 100 mg bid PLC	279.1 305.4	357.8 340.5	35.8 20.7	28.2 11.5
21-95-201	12	60 66	CLZ 100 mg bid PLC	122.7 124.6	158.3 161.8	32.7 30.6	29.0 29.9

Percent Mean Change from Pain –Free Walking Distance (ICD) from Baseline to End of Treatment

Study No.	Duration (wks)	Number of Patients (Efficacy ITT)	Treatment & Dosage	Mean at Baseline (m)	Mean at Endpoint (m)	Individual % change (mean)	Group % mean change
Pooled		1135 1131	CLZ 100 mg bid. PLC	91.4 95.3	153.3 135.8	74.5 51.3	67.8 42.6
21-92-202	24	140 140	CLZ 100 mg bid. PLC	70.4 72.4	137.9 95.5	91.6 40.6	95.9 31.8
21-94-201	24	124 125	CLZ 100 mg bid PLC	62.7 67.8	109.8 87.7	84.3 37.7	75.3 29.2
21-94-301	24	118 122	CLZ 100 mg bid PLC	77.7 83.0	130.0 129.6	59.5 72.9	67.3 56.2
21-96-202	24	205 226	CLZ 100 mg bid. PLC	124.1 128.6	217.7 202.2	98.3 68.4	75.4 57.2
21-98-213	24	231 218	CLZ 100 mg bid PLC	74.8 77.5	122.1 140.0	62.6 86.0	63.3 80.8
21-94-203	16	119 120	CLZ 100 mg bid PLC	128.8 140.4	205.6 187.9	68.3 38.5	59.6 33.9
21-90-201	16	52 25	CLZ 100 mg bid PLC	71.2 77.7	112.5 84.6	54.6 10.7	58.2 8.9
21-93-201	12	86 89	CLZ 100 mg bid PLC	133.8 147.8	194.5 203.3	57.5 52.2	45.4 37.5
21-95-201	12	60 66	CLZ 100 mg bid PLC	65.8 68.4	103.3 102.3	59.4 59.6	57.0 49.5

The Walking Impairment Questionnaire, which was administered in 7 of the nine clinical trials, assesses the impact of a therapeutic intervention on walking ability. In a pooled analysis of seven 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 calcium channel blockers.

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 0.33 mmol/L (15%) and an increase in HDL-cholesterol of 0.10mmol/L (10%).A randomized, double-blind, placebo-controlled Phase IV study (CASTLE) was conducted to assess the long-term effects of Pletal, with focus on mortality and safety. In total, 1,439 patients with intermittent claudication and no heart failure have been treated with Pletal or placebo for up to three years.

Baseline characteristics of the phase IV trial (CASTLE)

	Cilostazol Pletal (N = 721)	**Placebo (N = 718)**	**Total (N = 1439)**
Age (years)			
Mean (Min, Max)	66 (27,89)	65.9 (32,91)	66.2 (27, 91)
Gender			
Male	472 (65.5%)	470 (65.5%)	942 (65.5%)
Female	249 (34.5%)	248 (34.5%)	497 (34.5%)
Cigarette use			
Never	108 (15.0%)	99 (13.8%)	207 (14.4%)
Previous	407 (56.4%)	394 (54.9%)	801 (55.7%)
Current	206 (28.6%)	225 (31.3%)	431 (30.0%)
Diabetes mellitus	273 (37.9%)	242 (33.7%)	5.1 (35.8%)
Hypertension	595 (82.5%)	582 (81.1%)	1177 (81.8%)
MI: one or more	211 (29.3%)	208 (29%)	419 (29.1%)
Arrhythmia	124 (17.2%)	132 (18.4%)	256 (17.8%)
Palpitations	117 (16.2%)	133 (18.5%)	250 (17.4%)
Stroke	74 (10.3%)	76 (10.6%)	150 (10.4%)

In the CASTLE study with a total of 1435 subjects the incidence of bleeding adverse events was similar in cilostazol and placebo groups. 717 subjects were treated with cilostazol. 368 of these subjects (51.3%) received concomitant aspirin, 37 subjects (5.2%) received concomitant clopidogrel and 158 (22.0%) were treated concomitantly both with aspirin and clopidogrel. Doses of aspirin in the CASTLE study ranged from 80-650 mg/day with more than 50% of patients in the study taking doses of 325 mg/day or higher. Treatment-emergent bleeding events for patients taking concomitant clopidogrel and/or aspirin in the CASTLE study are summarised in the table below.

Parameter	Neither aspirin nor clopidogrel (N= 319)		Aspirin only (N= 723)		Clopidogrel only (N=86)		Both aspirin and clopidogrel (N=307)	
	CLZ (154)	PLC (165)	CLZ (368)	PLC (355)	CLZ (37)	PLC (49)	CLZ (158)	PLC (149)
Total No of bleeding AEs	9	21	21	27	0	10	27	22
No (%) of subjects with at least one bleeding AE	9 (5.8%)	14 (8.5%)	20 (5.4%)	24 (6.8%)	0	7 (14.3%)	21 (13.3%)	13 (8.7%)

CLZ = cilostazol; PLC = Placebo

With respect to mortality during CASTLE, the observed 36-month Kaplan-Meier event rate for deaths on study drug with a median time on study drug of 18 months was 5.6% (95% CI of 2.8 to 8.4%) on Pletal and 6.8% (95% CI of 1.9 to 11.5%) on placebo. Long-term treatment with Pletal did not raise safety concerns.

Pletal has not been studied in patients with rapidly progressing claudication or in patients with leg pain at rest, ischaemic leg ulcers or gangrene. Its long term effects on limb preservation and hospitalisation have not been evaluated. Similarly, there are no data on whether treatment with cilostazol results in a reduction in the number or frequency of adverse cardiovascular events

INDICATIONS

Pletal is indicated for the symptomatic improvement of intermittent claudication as indicated by increased maximal and pain-free walking distances in patients who do not have rest pain and who do not have evidence of peripheral tissue necrosis.

Pletal is for second-line use, in patients for whom lifestyle modifications (including stopping smoking and supervised exercise programs) and other appropriate interventions have failed to sufficiently improve their intermittent claudication symptoms.

CONTRAINDICATIONS

- Known hypersensitivity to Pletal or to any of the excipients
- Severe renal impairment: creatinine clearance of $\leq$ 25 ml/min
- Moderate or severe hepatic impairment
- Congestive heart failure of any grade or severity
- Pregnancy and lactation
- Patients taking inhibitors of CYP3A4 or of CYP2C19 (e.g. cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, omeprazole and inhibitors of HIV-1 proteases).
- Patients with a 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) or any active or uncontrolled bleeding
- Patients with a history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopic beats, whether or not adequately treated
- Patients with prolongation of the QTc interval
- Patients with a history of severe tachyarrhythmia
- Patients treated concomitantly with two or more additional antiplatelet or anticoagulant agents (eg acetylsalicylic acid, clopidogrel, heparin, warfarin, acenocoumarol, dabigatran, rivaroxaban or apixaban)
- Patients with unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months

PRECAUTIONS

The suitability of treatment with cilostazol should be carefully considered alongside other treatment options such as revascularisation.

Cardiovascular: Events of left ventricular outflow tract obstruction have been reported in patients with sigmoid shaped interventricular septum. Pletal should be used with caution in patients at risk, especially in elderly patients. Additional tests or an echocardiogram can be performed if the patient develops a de novo cardiac murmur after starting cilostazol.

Based on its mechanism of action, cilostazol may induce tachycardia, palpitation, tachyarrhythmia and/or hypotension. The increase in heart rate associated with cilostazol is approximately 5 to 7 bpm; in patients at risk this consequently may induce angina pectoris.

Patients who may be at increased risk for serious cardiac adverse events as a result of increased heart rate, e.g. patients with stable coronary disease, should be closely monitored during treatment with cilostazol, while the use of cilostazol in patients with unstable angina pectoris, or myocardial infarction/coronary intervention within the last 6 months, or a history of severe tachyarrhythmia is contraindicated.

Caution should be exercised when prescribing Pletal for patients with atrial or ventricular ectopy and patients with atrial fibrillation or flutter.

Caution is needed when co-administering Pletal with any other agent which has the potential to reduce blood pressure due to the possibility that there may be an additive hypotensive effect with a reflex tachycardia.

Hematologic: There have been rare or very rare reports of haematological abnormalities including thrombocytopenia, leucopenia, agranulocytosis, pancytopenia and aplastic anaemia and patients should be closely monitored. Most patients recovered on discontinuation of Pletal however, some cases of pancytopenia and aplastic anaemia were fatal. Pletal therapy should be stopped promptly upon the emergence of haematological abnormalities.

In addition to reporting episodes of bleeding and easy bruising, patients should be warned to promptly report any other signs which might also suggest the early development of blood dyscrasia such as pyrexia and sore throat. A full blood count should be performed if infection is suspected or there is any other clinical evidence of blood dyscrasia. Pletal should be discontinued promptly if there is clinical or laboratory evidence of haematological abnormalities.

Use in patients at risk of bleeding or with other antiplatelet agents: Patients treated with Pletal have an increased risk of bleeding which may be potentiated by co-administration with other agents with antiplatelet or anticoagulant properties. The patient should be warned to report any episode of bleeding or easy bruising whilst on therapy.

Due to Pletal's platelet aggregation inhibitory effect it is possible that an increased bleeding risk occurs in combination with surgery (including non invasive measures such as tooth extraction). If a patient is to undergo elective surgery and anti-platelet effect is not necessary, Pletal should be stopped 5 days prior to surgery.

In case of retinal bleeding administration of Pletal should be stopped.

Pletal is relatively highly protein bound and thus there is a theoretical potential that antiplatelet activity could be enhanced as a result of displacement by other highly protein bound drugs.

Cardiovascular toxicity: Repeat dose studies showed cardiovascular lesions in dogs at doses providing exposures below the clinical exposure based on AUC. Cardiovascular toxicity was manifested as haemorrhage and fibrosis of the myocardium and endocardium, arteritis and periarteritis, thickening of the coronary artery, smooth muscle degeneration in the tunica media and/or externa in dogs. The cardiovascular lesions were dose-related in dogs.

Effects on Fertility: There were no apparent effects of Pletal on the fertility of male or female rats at oral doses of up to 1000 mg/kg/day (equivalent to 1-5 times the clinical exposure based on AUC).

Use in Pregnancy: There is no experience of the use of Pletal in human pregnancy. Pletal should not be used by pregnant women.

Pregnancy Category B3

Studies in animals have shown reproductive toxicity. In rats dosed during pregnancy, an increase in foetuses with external, visceral and skeletal abnormalities (retarded ossification, wavy or extra ribs, ventricular septal defects, unilateral anophthalmia and dilated renal pelvis) were noted at doses >150 mg/kg/day (equivalent to 5 times the clinical exposure based on AUC). .Exposure in late pregnancy resulted in an increased incidence of stillbirths and lower offspring weights at the same doses. An increased incidence of retardation of ossification of the sternum was observed in rabbits at doses greater than 150 mg/kg/day (equivalent to 5 times the recommended daily dose based on AUC).

Use in Lactation: It is not known whether Pletal is excreted into human milk. The transfer of Pletal to breast milk has been reported in animal studies. Therefore Pletal should not be used by breastfeeding mothers.

Use in the Elderly: The pharmacokinetics of Pletal and its metabolites were not significantly affected by age or gender in healthy subjects aged between 50-80 years.

Genotoxicity: Pletal was not genotoxic in a battery of *in vitro* (bacterial reverse mutation in *Salmonella typhimurium* and *Escherichia coli* and forward mutation in mouse lymphoma cells) and *in vivo* (mouse micronucleus) assays. Increased chromosome aberrations occurred in an *in vitro* assay in Chinese hamster ovary cells, dependent on the incubation conditions. The weight of evidence from the assays suggests that Pletal presents no significant genotoxic potential at the proposed clinical dose.

Carcinogenicity: Two-year carcinogenicity studies have been conducted by the oral (dietary) route of administration in rats at doses up to 500 mg/kg/day, and in mice at doses up to 1000 mg/kg/day. Increased incidences of hepatocellular adenoma in female mice at 1000 mg/kg/day (0.7 times the clinical exposure based on AUC), and adrenal medullary adenoma in male rats at 500 mg/kg/day were documented (0.5 times the clinical exposure based on AUC). These tumours commonly occur in these animal species. The relevance to humans is unknown.

Effects on Laboratory Tests: There are no data with regard to effects on laboratory tests.

***Effects on Ability to Drive and Use Machines*:** Pletal may cause dizziness and patients should be warned to exercise caution before they drive or operate machinery.

INTERACTIONS WITH OTHER MEDICINES

Inhibitors of platelet aggregation: Pletal is a PDE III inhibitor with anti-platelet activity. In a clinical study in healthy subjects, Pletal 150mg b.i.d. for five days did not result in prolongation of bleeding time.

Aspirin: Short term (≤4 days) co-administration of aspirin with Pletal suggested a 23-25% increase in inhibition of ADP-induced *ex vivo* platelet aggregation when compared to aspirin alone. There was no additive or synergistic effect on arachidonic acid induced platelet aggregation when compared to aspirin alone.

There were no apparent trends toward a greater incidence of haemorrhagic adverse effects in patients taking Pletal and aspirin compared to patients taking placebo and equivalent doses of aspirin. Nonetheless, patients taking Pletal in combination with aspirin should be monitored for bleeding events.

Clopidogrel and other antiplatelet drugs: Concomitant administration of Pletal 150 mg b.i.d. and clopidogrel 75 mg daily for five days did not have a notable effect on the pharmacokinetics of Pletal, with an increase in AUC of only 9%. However, the AUC of the dehydro metabolite, which has about 4 times the potency of cilostazol in inhibiting platelet aggregation, increased by 24%. Concomitant administration of Pletal and clopidogrel did not have an appreciable effect on platelet count, prothrombin time (PT) or activated partial thromboplastin time (aPTT). All healthy subjects in the study had a prolongation of bleeding time on clopidogrel alone and concomitant administration with Pletal did not result in a significant additional effect on bleeding time. Caution is advised when co-administering Pletal with any drug that inhibits platelet aggregation. Consideration should be given to monitoring the bleeding time at intervals during co-administration. Pletal treatment is contraindicated in patients receiving two or more additional antiplatelet/anticoagulant agents. A higher rate of haemorrhage was observed with the concomitant use of clopidogrel, aspirin and cilostazol in the CASTLE trial.

Cilostazol has not been evaluated in circumstances where clopidogrel coadministration and a high bleeding risk co-exist, such as at the time of coronary stent insertion.

Anticoagulants: In a single-dose clinical study, no inhibition of the metabolism of warfarin or an effect on the coagulation parameters (PT, aPTT, bleeding time) was observed. However, caution is advised in patients receiving both Pletal and any anticoagulant agent, and frequent monitoring is required to reduce the possibility of bleeding. Pletal treatment is contraindicated in patients receiving two or more additional antiplatelet/anticoagulant agents.

Nitrates and PDE-5 Inhibitors: Drug interactions between Pletal and nitrates or Pletal and PDE-5 inhibitors used for erectile dysfunction (such as sildenafil, vardenafil or taldenafil) have not been specifically studied. Ten to fifteen percent of patients were on concomitant Pletal and nitrates in the clinical studies but no targeted safety analysis is available. Therefore, caution should be exercised during co-administration of Pletal with nitrates or PDE-5 inhibitors.

Cytochrome P-450 (CYP) enzyme inhibitors and substrates: Pletal is contraindicated in patients taking inhibitors of CYP3A4 or CYP2C19 and examples of the many drugs which are known to inhibit either of these isoenzymes are given in **CONTRAINDICATIONS.** It is recommended that caution be exercised during co-administration with substrates of CYP3A4 or CYP2C19 (e.g. cisapride, midazolam, nifedipine and verapamil) as this may result in increased plasma levels of these drugs.

Pletal is extensively metabolised by CYP enzymes, particularly CYP3A4 and to a lesser extent CYP2C19 and CYP2D6 although other enzymes are also involved. Some of the metabolites, particularly the dehydro metabolite, possess cilostazol-like activity. The effects of co-administration with CYP enzyme inhibitors are complex and Pletal is contraindicated in patients taking inhibitors of CYP3A4 or CYP2C19.

Pletal was shown to inhibit CYP3A4, CYP2C19 and CYP2C9 *in vitro*, but only at concentrations more than twice the plasma C_{max} at the recommended clinical dose.

Inhibitors and Substrates of CYP3A4: Co-administration of single doses of ketoconazole (strong inhibitor of CYP3A4 and inhibitor of 2C19) 400 mg and Pletal 100 mg resulted in a >2-fold increase in AUC of Pletal and increased systemic exposure to 4'-trans-hydroxy metabolite.

In healthy subjects dosed with Pletal 100 mg b.i.d., mean AUC Pletal increased by 44% on co-administration with diltiazem (CYP3A4 inhibitor) at 180 mg once daily. Co-administration did not affect exposure to the dehydro metabolite but there were increases in AUC of the 4'-trans-hydroxy metabolite. In patients in clinical trials, concomitant use with diltiazem was shown to increase the AUC of Pletal by 53%.

Administration of a single dose of 100 mg Pletal with 240 mL grapefruit juice (CYP3A4 inhibitor) did not have a notable effect on the pharmacokinetics of Pletal.

An interaction study with warfarin did not demonstrate significant effects on the pharmacokinetics of *R*-warfarin (CYP3A4 substrate) or *S*-warfarin (CYP2C9 substrate). However, the AUCs for lovastatin (CYP3A4 substrate) and its β-hydroxy acid were increased by more than 70% when given with Pletal. Caution is advised in cases of co-administration with statins metabolised by CYP3A4, for example simvastatin, atorvastatin and lovastatin.

Administration of 100 mg Pletal on the seventh day of erythromycin (moderate inhibitor of CYP3A4) 500 mg t.i.d. resulted in an increase in AUC Pletal by 74%, accompanied by a 24% decrease in AUC of the dehydro metabolite but with notable increases in AUC of the 4'-trans-hydroxy metabolite.

Inhibitors of CYP2C19: Administration of a single dose of 100 mg Pletal on day 7 of dosing with omeprazole 40 mg once daily increased C_{max} and AUC Pletal by 18% and 26%, respectively. Cmax and AUC of the dehydro metabolite increased by 29% and 69% while exposure to the 4'**-** trans-hydroxy metabolite decreased by 31%.

Inhibitors of CYP2D6: Concomitant administration of quinidine with a single dose of cilostazol 100 mg did not alter cilostazol pharmacokinetics.

ADVERSE EFFECTS

Clinical trials

The most commonly reported adverse reactions in clinical trials were headache (in > 30%), diarrhoea and abnormal stools (in >15% each). These reactions were usually of mild to moderate intensity and were sometimes alleviated by reducing the dose.

Adverse reactions reported as being at least possibly drug-related and occurring more commonly with Pletal 100 mg b.i.d. than in the placebo groups in clinical trials are listed below.

The frequencies correspond with:

Very common:	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1000)
Very rare	(<1/10,000)

Blood and the lymphatic system disorders

Common	Ecchymosis,
Uncommon	Anaemia
Rare	Bleeding time increased, thrombocythemia

Haemorrhagic disorders

Uncommon	Haemorrhages (eye, nose, gastrointestinal, cardiovascular)

Endocrine disorders

Uncommon	Diabetes mellitus

Metabolism and nutrition disorders

Common	Oedema (peripheral, face).
Uncommon	Hyperglycaemia

Nervous system disorders

Common	Dizziness
Uncommon	Insomnia, anxiety, abnormal dreams

Cardiac disorders

Common	Palpitation, tachycardia, angina pectoris, arrhythmia, ventricular extrasystoles
Uncommon	Myocardial infarction, atrial fibrillation, congestive heart failure, supraventricular tachycardia, ventricular tachycardia, syncope, postural hypotension

Respiratory, thoracic and mediastinal disorders

Common	Rhinitis, pharyngitis
Uncommon	Dyspnoea, pneumonia, cough

Gastrointestinal disorders

Very Common	Diarrhoea, abnormal stools
Common	Nausea and vomiting, dyspepsia, flatulence
Uncommon	Gastritis

Skin and subcutaneous tissue disorders

Common	Rash, pruritus

Musculoskeletal, connective tissue and bone disorders

Uncommon	Myalgia

Renal and urinary disorders

Rare	Kidney failure, kidney function abnormal

General disorders and administration site conditions

Very Common	Headache
Common	Chest pain, abdominal pain, asthenia
Uncommon	Chills, allergic reaction

An increase in the incidence of palpitation and peripheral oedema was observed when Pletal was combined with other vasodilators that cause reflex tachycardia e.g. dihydropyridine calcium channel blockers.

The only adverse event resulting in discontinuation of therapy in ≥3% of patients treated with Pletal was headache. Other frequent causes of discontinuation included palpitation and diarrhoea (both 1.1%).

Pletal *per se* may carry an increased risk of bleeding and this risk may be potentiated by co-administration with any other agent with such potential.

The risk of intraocular bleeding may be higher in patients with diabetes.

An increase in the frequency of diarrhoea and palpitation has been found in patients older than 70 years.

Post-marketing experience

Additional reactions not reported during clinical trials but reported rarely or very rarely in the post-marketing period are listed below.

Infections and infestations:	Interstitial pneumonia
Blood and the lymphatic system disorders:	Bleeding tendency, thrombocytopenia, granulocytopenia, agranulocytosis, leucopenia, pancytopenia, aplastic anaemia.
Cardiac disorders	Torsades de pointes, QTc prolongation occurred in patients with cardiac disorders, e.g. complete atrioventricular block, cardiac failure and bradyarrythmia when treated with Pletal (Pletal was used “off label” due to its positive chronotropic action).
Haemorrhagic disorders:	Haemorrhages (cerebral, respiratory tract, pulmonary, muscle)
Metabolism and nutrition disorders:	Anorexia
Nervous system disorders:	Paresis, hypaesthesia
Eye disorders:	Conjunctivitis
Ear and labyrinth disorders:	Tinnitus
Vascular disorders:	Hot flushes, hypertension, hypotension
Hepato-biliary disorders:	Hepatitis, hepatic function abnormal, jaundice
Gastrointestinal disorders:	Melena
Skin and subcutaneous tissue disorders:	Subcutaneous haemorrhage, eczema, skin eruptions including Stevens-Johnson syndrome or toxic epidermal necrolysis, urticaria
Renal and urinary disorder:	Haematuria, increased urinary frequency
General disorders and administration site conditions:	Pyrexia, malaise, pain
Investigations:	Uric acid level increased, BUN increased, blood creatinine increased

DOSAGE AND ADMINISTRATION

The recommended dosage of Pletal is 100 mg twice a day. Doses of 150 mg twice daily were investigated, however 100 mg twice daily provided the optimal risk to benefit ratio.

Pletal should be taken 30 minutes before or two hours after breakfast and the evening meal. Taking Pletal with food has been shown to increase the maximum plasma concentrations (C_{max}) of Pletal, which may be associated with an increased incidence of adverse effects.

Pletal treatment should be initiated by a physician experienced in the management of intermittent claudication. The patient should be reassessed after 3 months of treatment with a view to discontinuing Pletal where an inadequate effect is observed or symptoms have not improved.

Patients should continue with their lifestyle modifications (smoking cessation and exercise), and pharmacological interventions (such as lipid lowering and antiplatelet treatment) to reduce the risk of cardiovascular events. Pletal is not a substitute for such treatments.

Renal Insufficiency: No dose adjustment is necessary in patients with a creatinine clearance of >25 ml/min. Pletal is contraindicated in patients with a creatinine clearance of ≤ 25 ml/min.

Hepatic Insufficiency: No dosage adjustment is necessary in patients with mild hepatic disease. There are no data in patients with moderate or severe hepatic impairment. Since Pletal is extensively metabolised by hepatic enzymes, it is contraindicated in patients with moderate or severe hepatic impairment.

Paediatric use: Safety and efficacy in children have not been established.

Use in the Elderly: There are no special dosage requirements for the elderly.

OVERDOSAGE

Information on acute overdose in humans is limited. The signs and symptoms can be anticipated to be severe headache, diarrhoea, tachycardia and possibly cardiac arrhythmia.

Patients should be observed and given supportive treatment.

For advice on the management of overdosage, contact the Poisons Information Centre (Tel: 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

Pletal tablets are available as:

50 mg white, round, flat faced tablets debossed with “OG31” on one side, and
100 mg white, round, flat faced tablets debossed with “OG30” on one side.

Pletal Tablets are packed in PVC/Aluminium blisters in cartons containing 14, 56, 112 or 168 tablets

Not all presentations and pack sizes may be available in Australia.

Store below 25°C

NAME AND ADDRESS OF THE SPONSOR

Otsuka Australia Pharmaceutical Pty Ltd
Suite 2.03, Level 2
9 Help Street
Chatswood NSW 2067

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine: S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

29 January 2009

DATE OF MOST RECENT AMENDMENT

15 December 2017