Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pletal 50 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 50 mg of cilostazol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, flat faced tablets debossed with “OG31” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pletal is indicated for the improvement of the maximal and pain-free walking distances in patients with intermittent claudication, who do not have rest pain and who do not have evidence of peripheral tissue necrosis (peripheral arterial disease Fontaine stage II).

4.2 Posology and method of administration

The recommended dosage of cilostazol is 100 mg twice a day. Cilostazol should be taken 30 minutes before or two hours after breakfast and the evening meal. Taking cilostazol with food has been shown to increase the maximum plasma concentrations (Cmax) of cilostazol, which may be associated with an increased incidence of adverse effects.

Treatment for 16-24 weeks can result in a significant improvement in walking distance. Some benefit may be observed following treatment for 4-12 weeks.

The physician should consider other treatment options if cilostazol is ineffective after six months.

<u>The elderly</u>

There are no special dosage requirements for the elderly.

<u>Children</u>

Safety and efficacy in children have not been established.

<u>Renal impairment</u>

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

Hepatic impairment

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

4.3 Contraindications

- Known hypersensitivity to cilostazol or to any of the excipients
- Severe renal impairment: creatinine clearance of ≤ 25 ml/min
- Moderate or severe hepatic impairment
- Congestive heart failure
- Pregnancy
- Patients with any known predisposition to bleeding (e.g. active peptic ulceration, recent (within six months) haemorrhagic stroke, proliferative diabetic retinopathy, poorly controlled hypertension)
- Patients with any history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics, whether or not adequately treated, and in patients with prolongation of the QTc interval

4.4 Special warnings and precautions for use

Patients should be warned to report any episode of bleeding or easy bruising whilst on therapy. In case of retinal bleeding administration of cilostazol should be stopped. Refer to *Sections 4.3 Contraindications* and *4.5 Interactions with other medicinal products and other forms of interaction for further advice on bleeding.*

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

There have been rare or very rare reports of haematological abnormalities including thrombocytopenia, leucopenia, agranulocytosis, pancytopenia and aplastic anaemia *(see section 4.8).* Most patients recovered on discontinuation of cilostazol. However, some cases of pancytopenia and aplastic anaemia had a fatal outcome.

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. Cilostazol should be discontinued promptly if there is clinical or laboratory evidence of haematological abnormalities.

Caution is advised when cilostazol is co-administered with inhibitors or inducers of CYP3A4 and CYP2C19 or with CYP3A4 substrates. *See section 4.5 for further information.*

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

Caution is needed when co-administering cilostazol 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. *Refer also to Section 4.8.*

Caution should be exercised when co-administering cilostazol with any other agents that inhibit platelet aggregation. *Refer to section 4.5 Interactions with other medicinal products and other forms of interaction.*

4.5 Interaction with other medicinal products and other forms of interaction

Inhibitors of platelet aggregation

Cilostazol is a PDE III inhibitor with anti-platelet activity. In a clinical study in healthy subjects, cilostazol given 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 cilostazol suggested a 23-25% increase in inhibition of ADP-induced ex vivo platelet aggregation when compared to aspirin alone.

There were no apparent trends toward a greater incidence of haemorrhagic adverse effects in patients taking cilostazol and aspirin compared to patients taking placebo and equivalent doses
of aspirin.

Clopidogrel and other antiplatelet drugs

Concomitant administration of cilostazol and clopidogrel did not have any 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 cilostazol did not result in a significant additional effect on bleeding time. Caution is advised when co-administering cilostazol with any drug that inhibits platelet aggregation. Consideration should be given to monitoring the bleeding time at intervals. Special attention should be paid to patients who are receiving multiple anti-platelet therapies.

Oral Anticoagulants like warfarin

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 cilostazol and any anticoagulant agent, and frequent monitoring is required to reduce the possibility of bleeding.

Cytochrome P-450 (CYP) enzyme inhibitors

Cilostazol is extensively metabolised by CYP enzymes, particularly CYP3A4 and CYP2C19 and to a lesser extent CYP1A2. The dehydro metabolite, which has 4-7 times the potency of cilostazol in inhibiting platelet aggregation, appears to be formed primarily via CYP3A4.

The 4`-trans-hydroxy metabolite, with potency one-fifth that of cilostazol, appears to be formed primarily via CYP2C19. Therefore, drugs inhibiting CYP3A4 (e.g., some macrolides, azole antifungals, protease inhibitors) or CYP2C19 (like proton pump inhibitors, PPIs) increase the total pharmacological activity by 32 and 42%, respectively and could have the potential to enhance the undesirable effects of cilostazol. A dose reduction to cilostazol 50 mg b.i.d. could be considered based on the individual clinical and tolerance response. Administration of 100 mg cilostazol on the seventh day of erythromycin (a moderate inhibitor of CYP3A4) 500 mg t.i.d. resulted in an increase in the AUC of cilostazol 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.

Co-administration of single doses of ketoconazole (a strong inhibitor of CYP3A4) 400 mg and cilostazol 100 mg resulted in a 117% increase in the AUC of cilostazol, accompanied by a 15% decrease in the AUC of the dehydro metabolite and a 87% increase in the AUC of the 4`-trans-hydroxy metabolite, which finally increases the total pharmacological activity by 32% as compared to cilostazol alone.

Administration of 100 mg cilostazol b.i.d. with diltiazem (an inhibitor of CYP3A4) 180 mg once daily resulted in an increase in the AUC of cilostazol by 44%. Co-administration did not affect exposure to the dehydro metabolite but increased by 40% the AUC of the 4`-trans-hydroxy metabolite. In patients in clinical trials, concomitant use with diltiazem was shown to increase the AUC of cilostazol by 53%.

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

Administration of a single dose of 100 mg cilostazol on the seventh day of omeprazole (an inhibitor of CYP2C19) 40 mg once daily increased the AUC of cilostazol by 26%, accompanied by a 69% increase in the AUC of the dehydro metabolite and a decrease of 31% in the AUC of the 4`-trans hydroxy metabolite, which finally increases the total pharmacological activity by 42% as compared to cilostazol alone.

Cytochrome P-450 enzyme substrates

Cilostazol has been shown to increase the AUC of lovastatin (sensitive substrate for CYP3A4) and its β-hydroxy acid by 70%. Caution is advised when cilostazol is co-administered with CYP3A4 substrates with a narrow therapeutic index (e.g., cisapride, halofantrine, pimozide, ergot derivates). Caution is advised in case of co-administration with simvastatin.

Cytochrome P-450 enzyme inducers

The effect of CYP3A4 and CYP2C19 inducers (such as carbamazepin, phenytoin, rifampicin and St. John's wort) on cilostazol pharmacokinetics has not been evaluated. The antiplatelet effect may theoretically be altered and should be carefully monitored when cilostazol is co-administered with CYP3A4 and CYP2C19 inducers.

In clinical trials, smoking (which induces CYP1A2) decreased cilostazol plasma concentrations by 18%.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data in the use of cilostazol in pregnant women. Studies in animals have shown reproductive toxicity *(see Section 5.3).* The potential risk for humans is unknown. Pletal should not be used during pregnancy.

Lactation

The transfer of cilostazol to breast milk has been reported in animal studies. The excretion of cilostazol in human milk is unknown. Due to the potential harmful effect in the newborn child breast fed by a treated mother, the use of Pletal is not recommended during breast feeding.

4.7 Effects on ability to drive and use machines

Cilostazol may cause dizziness and patients should be warned to exercise caution before they drive or operate machinery.

4.8 Undesirable effects

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 in clinical trials and in the post-marketing period are included in the table 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), not known (cannot be estimated from the available data)

The frequencies of reactions observed in the post-marketing period is considered unknown (cannot be estimated from the available data).

Blood and the lymphatic system disorders	*Common* *Uncommon* *Rare* *Unknown*	Ecchymosis Anaemia Bleeding time prolonged, thrombocythaemia Bleeding tendency, thrombocytopenia, granulocytopenia, agranulocytosis, leukopenia, pancytopenia, aplastic anaemia
Immune system disorders	*Uncommon*	Allergic reaction
Metabolism and nutrition disorders	*Common* *Uncommon* *Unknown*	Oedema (peripheral, face) Hyperglycaemia, Diabetes mellitus Anorexia
Psychiatric disorders	*Uncommon*	Anxiety
Nervous system disorders	*Very common* *Common* *Uncommon* *Unknown*	Headache Dizziness Insomnia, abnormal dreams Paresis, hypoaesthesia
Eye disorders	*Unknown*	Conjunctivitis
Ear and labyrinth disorders	*Unknown*	Tinnitus
Cardiac disorders	*Common*	Palpitation, tachycardia, angina pectoris, arrhythmia, ventricular extrasystoles
	Uncommon	Myocardial infarction, atrial fibrillation, congestive heart failure, supraventricular tachycardia, ventricular tachycardia, syncope
Vascular disorders	*Uncommon*	Eye haemorrhage, epistaxis, gastrointestinal haemorrhage, haemorrhage unspecified, orthostatic hypotension
	Unknown	Hot flushes, hypertension, hypotension, cerebral haemorrhage, pulmonary haemorrhage, muscle haemorrhage, respiratory tract haemorrhage, subcutaneous haemorrhage
Respiratory, thoracic and mediastinal disorders	*Common* *Uncommon* *Unknown*	Rhinitis, pharyngitis Dyspnoea, pneumonia, cough Interstitial pneumonia
Gastrointestinal disorders	*Very common* *Common* *Uncommon*	Diarrhoea, abnormal faeces Nausea and vomiting, dyspepsia, flatulence, abdominal pain Gastritis
Hepato-biliary disorders	*Unknown*	Hepatitis, hepatic function abnormal, jaundice

Skin and subcutaneous tissue disorders	*Common* *Unknown*	Rash, pruritus Eczema, skin eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
Musculoskeletal, connective tissue and bone disorders	*Uncommon*	Myalgia
Renal and urinary disorders	*Rare* *Unknown*	Renal failure, renal impairment Haematuria, pollakiuria
General disorders and administration site conditions	*Common* *Uncommon* *Unknown*	Chest pain, asthenia Chills Pyrexia, malaise, pain
Investigations	*Unknown*	Uric acid level increased, blood urea increased, blood creatinine increased

An increase in the incidence of palpitation and peripheral oedema was observed when cilostazol 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 cilostazol was headache. Other frequent causes of discontinuation included palpitation and diarrhoea (both 1.1%).

Cilostazol per se may carry an increased risk of bleeding and this risk may be potentiated by coadministration with any other agent with such potential.

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

4.9 Overdose

Information on acute overdose in humans is limited. The signs and symptoms can be anticipated to be severe headache, diarrhoea, tachycardia and possibly cardiac arrhythmias. Patients should be observed and given supportive treatment. The stomach should be emptied by induced vomiting or gastric lavage, as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitor excl. heparin. ATC code: B01A C

From data generated in nine placebo-controlled studies (where 1,634 patients were exposed to cilostazol), it has been demonstrated that cilostazol 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, cilostazol 100 mg b.i.d. increases in mean ACD ranged from 60.4 - 129.1 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 cilostazol 100 mg b.i.d. over the improvement seen under placebo. This corresponds to a relative improvement of 100% over placebo. This effect appeared lower in diabetics than in non-diabetics.

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

Studies in animals and in man (in vivo and ex vivo) have shown that cilostazol causes reversible 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 cilostazol recovery of aggregation occurred within 48-96 hours, without rebound hyperaggregability. 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 was conducted to assess the long-term effects of cilostazol, with focus on mortality and safety. In total, 1,439 patients with intermittent claudication and no heart failure have been treated with cilostazol or placebo for up to three years. With respect to mortality, 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 cilostazol and 6.8% (95% CI of 1.9 to 11.5%) on placebo. Long-term treatment with cilostazol did not raise safety concerns.

5.2 Pharmacokinetic properties

Following multiple doses of cilostazol 100 mg twice daily in patients with peripheral vascular disease, steady state is achieved within 4 days.

The Cmax of cilostazol and its primary circulating metabolites increase less than proportionally with increasing doses. However, the AUC for cilostazol and its metabolites increase approximately proportionately with dose.

The apparent elimination half-life of cilostazol is 10.5 hours. There are two major metabolites, a dehydrocilostazol and a 4’-trans-hydroxy cilostazol, both of which have similar apparent half-lives. The dehydro metabolite is 4-7 times as active a platelet anti-aggregant as the parent compound and the 4’-trans-hydroxy metabolite is one fifth as active. Plasma concentrations (as measured by AUC) of the dehydro and 4`-transhydroxy metabolites are ~41% and ~12% of cilostazol concentrations.

Cilostazol 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 to an even lesser extent CYP1A2.

The primary route of elimination is urinary (74%) with the remainder excreted in the faeces. No measurable amount of unchanged cilostazol 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.

Cilostazol is 95-98% protein bound, predominantly to albumin. The dehydro metabolite and 4’-transhydroxy metabolite are 97.4% and 66% protein bound respectively.

There is no evidence that cilostazol induces hepatic microsomal enzymes.

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

In subjects with severe renal impairment, the free fraction of cilostazol was 27% higher and both Cmax and AUC were 29% and 39% lower respectively than in subjects with normal renal function. The Cmax 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 Cmax and AUC of 4'-trans-hydroxy cilostazol were 173% and 209% greater in subjects with severe renal impairment. The drug should not be administered to patients with a creatinine clearance <25ml/min *(see Section 4.3).*

There are no data in patients with moderate to severe hepatic impairment and since cilostazol is extensively metabolised by hepatic enzymes, the drug should not be used in such patients *(see Section 4.3).*

5.3 Preclinical safety data

Cilostazol and several of its metabolites are phosphodiesterase III inhibitors which suppress cyclic AMP degradation, resulting in increased cAMP in a variety of tissues including platelets and blood vessels. As with other positive inotropic and vasodilator agents, cilostazol produced cardiovascular lesions in dogs. Such lesions were not seen in rats or monkeys and are considered species specific. Investigation of QTc in dogs and monkeys showed no prolongation after administration of cilostazol or its metabolites. Mutagenicity studies were negative in bacterial gene mutation, bacterial DNA repair, mammalian cell gene mutation and mouse *in vivo* bone marrow chromosomal aberrations. In *in vitro* tests on Chinese ovary hamster cells cilostazol produced a weak but significant increase in chromosome aberration frequency. No unusual neoplastic outcomes were observed in two-year carcinogenicity studies in rats at oral (dietary) doses up to 500 mg/kg/day, and in mice at doses up to 1000 mg/kg/day.

In rats dosed during pregnancy, foetal weights were decreased. In addition, an increase in foetuses with external, visceral and skeletal abnormalities was noted at high dose levels. At lower dose levels, retardations of ossification were observed. Exposure in late pregnancy resulted in an increased incidence of stillbirths and lower offspring weights. An increased incidence of retardation of ossification of the sternum was observed in rabbits. As there is no experience of cilostazol use in human pregnancy, it should not be used in women who are pregnant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, microcrystalline cellulose, carmellose calcium, hypromellose and magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Cartons containing 14, 20, 28, 30, 50, 56, 98, 100, 112 and 168 tablets as well as hospital packs with 70 (5x14) tablets packed in PVC/Aluminium blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 0985/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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