Annex III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cilostazol-containing medicinal product (see Annex I) 50 mg tablets
Cilostazol-containing medicinal product (see Annex I) 100 mg tablets

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 50 mg of cilostazol.
One tablet contains 100 mg of cilostazol.

For a full list of excipients, see section 6.1.

[To be completed nationally]

3. PHARMACEUTICAL FORM

Tablet

White, round, flat faced tablets debossed with "OG31" on one side.
White, round, flat faced tablets debossed with "OG30" on one side.

4.1 Therapeutic indications

<Cilostazol-containing medicinal product> 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).
<Cilostazol-containing medicinal product> is for second-line use, in patients in whom lifestyle modifications (including stopping smoking and [supervised] exercise programs) and other appropriate interventions have failed to sufficiently improve their intermittent claudication symptoms.

4.2 Posology and method of administration

Posology

The recommended dosage of cilostazol is 100 mg twice a day. Cilostazol should be taken 30 minutes before breakfast and the evening meal. Taking cilostazol with food has been shown to increase the maximum plasma concentrations (C_{max}) of cilostazol, which may be associated with an increased frequency of adverse reactions.

Cilostazol should be initiated by physicians experienced in the management of intermittent claudication (see also section 4.4).

The physician should reassess the patient after 3 months of treatment with a view to discontinuing cilostazol where an inadequate effect is observed or symptoms have not been improved.
Patients receiving treatment with cilostazol should continue with their life-style modifications (smoking cessation and exercise), and pharmacological interventions (such as lipid lowering and antiplatelet treatment) to reduce the risk of cardiovascular events. Cilostazol is not a substitute for such treatments.

Reduction of the dose to 50 mg twice daily is recommended in patients receiving medicines that strongly inhibit CYP3A4, for example some macrolides, azole antifungals, protease inhibitors, or medicines that strongly inhibit CYP2C19, for example omeprazole (see sections 4.4 and 4.5).

The elderly

There are no special dosage requirements for the elderly.

Paediatric population

Safety and efficacy in children have not been established.

Renal impairment

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
- Patients with a history of severe tachyarrhythmia
- Patients treated concomitantly with two or more additional antiplatelet or anticoagulant agents (e.g. 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.

4.4 Special warnings and precautions for use

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

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 (see section 4.3).

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

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 and 4.5 for further information on bleeding risks.
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 antiplatelet 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.

In the case of patients receiving strong inhibitors for CYP3A4 or CYP2C19, plasma levels of cilostazol were shown to be increased. In such cases, a cilostazol dosage of 50 mg twice daily is recommended (see section 4.5 for further information).

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 sections 4.3 and 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

Inhibitors of platelet aggregation

Cilostazol is a PDE III inhibitor with antiplatelet 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.

Acetylsalicylic Acid (ASA)

Short term (≤4 days) co-administration of ASA with cilostazol suggested a 23-25% increase in inhibition of ADP-induced *ex vivo* platelet aggregation when compared to ASA alone.

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

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. Cilostazol treatment is contraindicated in patients receiving two or more additional antiplatelet/anticoagulant agents (see section 4.3).
A higher rate of haemorrhage was observed with the concomitant use of clopidogrel, ASA and cilostazol in the CASTLE trial.

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.
Cilostazol treatment is contraindicated in patients receiving two or more additional antiplatelet/anticoagulant agents (see section 4.3).

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 and could have the potential to enhance the undesirable effects of cilostazol. Consequently, for patients concomitantly taking strong CYP3A4 or CYP2C19 inhibitors the recommended dose is 50 mg twice daily (see section 4.2).

Administration of cilostazol with erythromycin (an inhibitor of CYP3A4) resulted in an increase in the AUC of cilostazol by 72%, accompanied by a 6% increase in AUC of the dehydro metabolite and a 119% increase in AUC of the 4`-trans-hydroxy metabolite.
Based on AUC, the overall pharmacological activity of cilostazol increases 34% when co-administered with erythromycin. Based on these data, the recommended dose of cilostazol is 50 mg bid in the presence of erythromycin and similar agents (e.g., clarithromycin).

Co-administration of ketoconazole (an inhibitor of CYP3A4 with cilostazol 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. Based on AUC, the overall pharmacological activity of cilostazol increases 35% when co-administered with ketoconazole. Based on these data, the recommended dose of cilostazol is 50 mg bid in the presence of ketoconazole and similar agents (e.g., itraconazole).

Administration of cilostazol with diltiazem (a weak inhibitor of CYP3A4) resulted in an increase in the AUC of cilostazol of 44%, accompanied by a 4% increase in AUC of the dehydro metabolite and a 43% increase in the AUC of the 4`-trans-hydroxy metabolite.
Based on AUC, overall pharmacological activity of cilostazol increases 19 % when co-administered with diltiazem. Based on these data, no dose adjustment is necessary.

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. Based on these data, no dose adjustment is necessary. A clinically relevant effect on cilostazol is still possible at higher quantities of grapefruit juice.

Administration of cilostazol with omeprazole (an inhibitor of CYP2C19) increased the AUC of cilostazol by 22%, accompanied by a 68% increase in the AUC of the dehydro metabolite and a decrease of 36% in the AUC of the 4`-trans hydroxy metabolite. Based on AUC, the overall pharmacological activity increases by 47% when co-administered with omeprazole. Based on these data, the recommended dose of cilostazol is 50 mg bid in the presence of omeprazole.

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 statins metabolised by CYP3A4, for example simvastatin, atorvastatin and lovastatin.

Cytochrome P-450 enzyme inducers

The effect of CYP3A4 and CYP2C19 inducers (such as carbamazepine, 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%.

Other potential interactions

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.

4.6 Fertility, 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. <Cilostazol-containing medicinal product> must not be used during pregnancy (see section 4.3).

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 <Cilostazol-containing medicinal product> is not recommended during breast feeding.

Fertility

Cilostazol did not alter fertility in animal studies.

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 are considered unknown (cannot be estimated from the available data).

Blood and the lymphatic system disorders	Common	Ecchymosis
	Uncommon	Anaemia
	Rare	Bleeding time prolonged, thrombocythaemia
	Unknown	Bleeding tendency, thrombocytopenia, granulocytopenia, agranulocytosis, leukopenia, pancytopenia, aplastic anaemia
Immune system disorders	Uncommon	Allergic reaction
Metabolism and nutrition disorders	Common	Oedema (peripheral, face), anorexia
	Uncommon	Hyperglycaemia, Diabetes mellitus
Psychiatric disorders	Uncommon	Anxiety
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Insomnia, abnormal dreams
	Unknown	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	Rhinitis, pharyngitis
	Uncommon	Dyspnoea, pneumonia, cough
	Unknown	Interstitial pneumonia
Gastrointestinal disorders	Very common	Diarrhoea, abnormal faeces
	Common	Nausea and vomiting, dyspepsia, flatulence, abdominal pain
	Uncommon	Gastritis
Hepato-biliary disorders	Unknown	Hepatitis, hepatic function abnormal, jaundice
Skin and subcutaneous tissue disorders	Common	Rash, pruritus
	Unknown	Eczema, skin eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
Musculoskeletal, connective tissue and bone disorders	Uncommon	Myalgia
Renal and urinary disorders	Rare	Renal failure, renal impairment
	Unknown	Haematuria, pollakiuria
General disorders and administration site conditions	Common	Chest pain, asthenia
	Uncommon	Chills, malaise
	Unknown	Pyrexia, pain
Investigations	Unknown	Uric acid level increased, blood urea increased, blood creatinine increased

An increase in the frequency 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 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.

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 <Cilostazol-containing medicinal product>. After 12 weeks, as compared to placebo, <Cilostazol-containing medicinal product> 100 mg b.i.d. produced a reduction in triglycerides of 0.33 mmol/l (15%) and an increase in HDL-cholesterol of 0.10 mmol/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 C_{max} 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 dehydro-cilostazol 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 antiaggregant 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`-trans-hydroxy 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'-trans-hydroxy 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 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. The medicine must 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 medicine must 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 frequency of stillbirths and lower offspring weights. An increased frequency of retardation of ossification of the sternum was observed in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, microcrystalline cellulose, carmellose calcium, hypromellose and magnesium stearate.
[To be completed nationally]

6.2 Incompatibilities

Not applicable.
[To be completed nationally]

6.3 Shelf life

3 years.
[To be completed nationally]

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
[To be completed nationally]

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.
[To be completed nationally]

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Cilostazol-containing medicinal products (see Annex I) 50 mg tablets
Cilostazol-containing medicinal products (see Annex I) 100 mg tablets

[See Annex I - To be completed nationally]

Cilostazol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One tablet contains 50 mg of cilostazol.
One tablet contains 100 mg of cilostazol.

[To be completed nationally]

3. LIST OF EXCIPIENTS

{Not applicable.}
[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

20 tablets
28 tablets
30 tablets
50 tablets
56 tablets
100 tablets
112 tablets
168 tablets

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

{Not applicable.}

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

{Not applicable.}

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

{Not applicable.}

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]
[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medicinal prescription
[To be completed nationally]

15. INSTRUCTIONS ON USE

{Not applicable}

16. INFORMATION IN BRAILLE

<Cilostazol-containing medicinal product> 50 mg
<Cilostazol-containing medicinal product> 100 mg
[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{Blister}

1. NAME OF THE MEDICINAL PRODUCT

Cilostazol-containing medicinal products (see Annex I) 50 mg tablets
Cilostazol-containing medicinal products (see Annex I) 100 mg tablets

[See Annex I - To be completed nationally]

Cilostazol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

{Not applicable}

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cilostazol-containing medicinal products (see Annex I) 50 mg tablets
Cilostazol-containing medicinal products (see Annex I) 100 mg tablets
Cilostazol
[See Annex I - To be completed nationally]

Cilostazol

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT <CILOSTAZOL-CONTAINING MEDICINAL PRODUCT> IS AND WHAT IT IS USED FOR

<Cilostazol-containing medicinal product> belongs to a group of medicines called phosphodiesterase type 3 inhibitors.
It has several actions which include widening of some blood vessels and reducing the clotting activity (clumping) of some blood cells called platelets inside your vessels.

You have been prescribed <Cilostazol-containing medicinal product> for "intermittent claudication". Intermittent claudication is the cramp-like pain in your legs when you walk and is caused by insufficient blood supply in your legs. <Cilostazol-containing medicinal product> can increase the distance you can walk without pain since it improves the blood circulation in your legs. Cilostazol is only recommended for patients whose symptoms have not improved sufficiently after making life-style modifications (such as stopping smoking and increasing exercise) and after other appropriate interventions. It is important that you continue the modifications you have made to your life-style whilst taking cilostazol.

2. BEFORE YOU TAKE <CILOSTAZOL-CONTAINING MEDICINAL PRODUCT>

Do not take <Cilostazol-containing medicinal product>
- if you are allergic (hypersensitive) to cilostazol or any of the other ingredients of <Cilostazol-containing medicinal product>.
- if you have the condition "heart failure".
- if you have persistent chest pain at rest, or have had a "heart attack" or any heart surgery in the last six months
- if you have now or previously suffered from blackouts due to heart disease, or any severe disturbances of the heart beat.
- if you know that you have a condition which increases your risk of bleeding or bruising, such as:
  - active stomach ulcer(s).
  - stroke in the past six months.
  - problems with your eyes if you have diabetes.
  - if your blood pressure is not well controlled.

if you are taking both acetylsalicylic acid and clopidogrel, or any combination of two or more medicines which can increase your risk of bleeding [ask your doctor or pharmacist if you are not sure]
- if you have severe kidney disease or moderate or severe liver disease.
- if you are pregnant

Take special care with <Cilostazol-containing medicinal product>
Before taking <Cilostazol-containing medicinal product> make sure your doctor knows:
- if you have a severe heart problem or any problems with your heart beat.
- if you have problems with your blood pressure.

During treatment with <Cilostazol-containing medicinal product> make sure that
- If you need to have surgery including having teeth removed, tell your doctor or dentist that you are taking <Cilostazol-containing medicinal product>.
- If you experience easy bruising or bleeding, stop taking <Cilostazol-containing medicinal product> and tell your doctor.

Taking other medicines
Before you start taking <Cilostazol-containing medicinal product>, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should specifically inform your doctor if you take some medicines usually used to treat painful and/or inflammatory conditions of muscle or joints, or if you take medicines to reduce blood clotting. These medicines include:
- acetylsalicylic acid
- clopidogrel
- anticoagulant medicines (e.g. warfarin, dabigatran, rivaroxaban, apixaban or low molecular weight heparins).

If you are taking such medicines with <Cilostazol-containing medicinal product> your doctor may perform some routine blood tests.

Certain medicines may interfere with the effect of <Cilostazol-containing medicinal product> when taken together. They may either increase the side effects of <Cilostazol-containing medicinal product> or make <Cilostazol-containing medicinal product> less effective. <Cilostazol-containing medicinal product> may do the same to other medicines. Before you start taking <Cilostazol-containing medicinal product>, please tell your doctor if you are taking:
- erythromycin, clarithromycin or rifampicin (antibiotics)
- ketoconazole (to treat fungal infections)
- omeprazole (to treat excess acid in the stomach)
- diltiazem (to treat high blood pressure or chest pain)
- cisapride (to treat stomach disorders)
- lovastatin, simvastatin or atorvastatin (to treat high cholesterol in the blood)
- halofantrine (to treat malaria)
- pimozide (to treat mental illnesses)
- ergot derivatives (to treat migraine, e.g. ergotamine, dihydroergotamine)
- carbamazepine or phenytoin (to treat convulsions)
- St. John's wort (a herbal remedy)

If you are not sure if this applies to your medicines ask your doctor or pharmacist.

Before you start taking <Cilostazol-containing medicinal product>, please inform your doctor if you are taking medicines for high blood pressure because <Cilostazol-containing medicinal product> may have an additional lowering effect on your blood pressure. If your blood pressure falls too low, this could cause a fast heartbeat. These medicines include:
- Diuretics (e.g., hydrochlorothiazide, furosemide)
- calcium channel blockers (e.g., verapamil, amlodipine)
- ACE inhibitors (e.g., captopril, lisinopril)
- angiotensin II receptor blockers (e.g., valsartan, candesartan)
- beta blockers (e.g., labetalol, carvedilol);

It may still be all right for you to take the above mentioned medicines and <Cilostazol-containing medicinal product> together and your doctor will be able to decide what is suitable for you.

Taking <Cilostazol-containing medicinal product> with food and drink
<Cilostazol-containing medicinal product> tablets should be taken 30 minutes before breakfast and the evening meal.
Always take your tablets with a drink of water.

Pregnancy and breast-feeding
<Cilostazol-containing medicinal product> **MUST NOT** be used during pregnancy.
For breast-feeding mothers use of <Cilostazol-containing medicinal product> is **NOT RECOMMENDED**.

If you are pregnant, think you may be pregnant or if you are breast-feeding ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
<Cilostazol-containing medicinal product> may cause dizziness. If you feel dizzy after taking <Cilostazol-containing medicinal product> tablets, **DO NOT** drive and do not use any tools or machines and inform your doctor or pharmacist.

3. HOW TO TAKE <CILOSTAZOL-CONTAINING MEDICINAL PRODUCT>

- Always take <Cilostazol-containing medicinal product> exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- The usual dose is two 50 mg tablets twice a day (morning and evening). This dose does not need to be changed for elderly people. However, your doctor may prescribe a lower dose if you are taking other medicines which may interfere with the effect of <Cilostazol-containing medicinal product>.
- The usual dose is one 100 mg tablet twice a day (morning and evening). This dose does not need to be changed for elderly people. However, your doctor may prescribe a lower dose if you are taking other medicines which may have an effect on <Cilostazol-containing medicinal product>.
- <Cilostazol-containing medicinal product> tablets should be taken 30 minutes before breakfast and the evening meal. Always take your tablets with a drink of water.

Some benefits of taking <Cilostazol-containing medicinal product> may be felt within 4-12 weeks of treatment. Your doctor will assess your progress after 3 months of treatment and may recommend that you discontinue cilostazol if the effect of treatment is insufficient.

<Cilostazol-containing medicinal product> is not suitable for children.

If you take more <Cilostazol-containing medicinal product> than you should
If for any reason you have taken more <Cilostazol-containing medicinal product> tablets than you should, you may have signs and symptoms such as severe headache, diarrhoea, a fall in blood pressure and irregularities of your heartbeat.

If you have taken more tablets than your prescribed dose, contact your doctor or your local hospital immediately. Remember to take the pack with you so that it is clear what medicine you have taken.

If you forget to take <Cilostazol-containing medicinal product>
If you miss a dose, do not worry; wait until the next dose to take your next tablet and then carry on as normal. **DO NOT** take a double dose to make up for a forgotten tablet.

If you stop taking <Cilostazol-containing medicinal product>
If you stop taking <Cilostazol-containing medicinal product> the pain in your legs may come back or get worse. Therefore, you should only stop taking <Cilostazol-containing medicinal product> if you notice side effects requiring urgent medical attention (see section 4) or if your doctor tells you to.

4. POSSIBLE SIDE EFFECTS

Like all medicines, <Cilostazol-containing medicinal product> can cause side effects, although not everybody gets them.

If any of the following side effects happen, you may need urgent medical attention. Stop taking <Cilostazol-containing medicinal product> and contact a doctor or go to the nearest hospital immediately.
- stroke
- heart attack
- heart problems which can cause shortness of breath or ankle swelling
- irregular heart beat (new or worsening)

- noticeable bleeding
- easy bruising
- serious illness with blistering of the skin, mouth, eyes and genitals
- yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice)

You should also tell your doctor immediately if you have a fever or sore throat. You may need to have some blood tests and your doctor will decide on your further treatment.

The following side effects have been reported for <Cilostazol-containing medicinal product>. You should tell your doctor as soon as possible:

Very common side effects (affecting more than 1 in 10 people)
- headache
- abnormal stools
- diarrhoea

Common side effects (affecting less than 1 in 10, but more than 1 in 100 people)
- fast heart beat
- heart pounding (palpitation)
- chest pain
- dizziness
- sore throat
- runny nose (rhinitis)
- abdominal pain
- abdominal discomfort (indigestion)
- feeling or being sick (nausea or vomiting)
- loss of appetite (anorexia)
- excessive burping or wind (flatulence)
- swelling of ankles, feet or face
- rash or changes in appearance of the skin
- itchy skin
- patchy bleeding in the skin
- general weakness

Uncommon side effects (affecting less than 1 in 100, but more than 1 in 1,000 people)
- heart attack
- irregular heart beat (new or worsening)
- heart problems that can cause shortness of breath or ankle swelling
- pneumonia
- cough
- chills
- unexpected bleeding
- tendency to bleed (e.g., of the stomach, eye or muscle, nose bleed and blood in spit or urine)
- decrease in red cells in the blood
- dizziness on standing up
- fainting
- anxiety
- difficulty sleeping
- unusual dreams
- allergic reaction
- aches and pains
- diabetes and increased blood sugar
- stomach ache (gastritis)
- malaise

There may be a higher risk of bleeding into the eye in people with diabetes.

Rare side effects (affecting less than 1 in 1,000, but more than 1 in 10,000 people):
- tendency to bleed for longer than usual
- increase in the platelets in the blood
- problems with the kidneys

The following side effects have been reported during the use of <Cilostazol-containing medicinal product> but it is not known how frequently they may occur:

- changes in the blood pressure
- decrease in red cells, white cells and platelets in your blood
- difficulty breathing
- difficulty moving
- fever
- hot flushes
- eczema and other skin rashes
- reduced sensation of the skin
- runny or sticky eyes (conjunctivitis)
- ringing in the ears (tinnitus)
- liver problems including hepatitis
- changes in the urine

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE <CILOSTAZOL-CONTAINING MEDICINAL PRODUCT>

Keep <Cilostazol-containing medicinal product> out of the reach and sight of children.

Do not use <Cilostazol-containing medicinal product> after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last date of the month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What <Cilostazol-containing medicinal product> contains
- The active substance is cilostazol. One tablet contains 50 mg cilostazol.
- The active substance is cilostazol. One tablet contains 100 mg cilostazol.
- The other ingredients are maize starch, microcrystalline cellulose, carmellose calcium, hypromellose and magnesium stearate.
  [To be completed nationally]

What <Cilostazol-containing medicinal product> looks like and contents of the pack
The <Cilostazol-containing medicinal product> 50 mg tablet is a white, round, flat-faced tablet, debossed with "OG31" on one side.
The <Cilostazol-containing medicinal product> 100 mg tablet is a white, round, flat-faced tablet, debossed with "OG30" on one side.
Your medicine is supplied in packs of 14, 20, 28, 30, 50, 56, 98, 100, 112 or 168 tablets or hospital packs with 70 (5x14) tablets.
Not all pack sizes may be marketed.
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

Manufacturer
[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:
[See Annex I - To be completed nationally]

This leaflet was last revised in <{MM/YYYY}>.
[To be completed nationally]