Front

CILOSTAZOL

CILOZOL-50/100

(50 mg/100 mg Tablet)

ANTITHROMBOTIC AGENT

Product Name:
Cilostazol

Name and Strength of Active Ingredient (s):
Cilostazol Tablets USP 50/100mg

Product Description: White to off white colored, circular shaped, biconvex, uncoated tablets, with both the faces plain.

Pharmacodynamics / Pharmacokinetics:
Pharmacodynamics:
Cilostazol reversibly inhibits platelet aggregation induced by a variety of stimuli, including thrombin, ADP, collagen, arachidonic acid, epinephrine, and shear stress. Effects on circulating plasma lipids have been examined in patients taking cilostazol. After 12 weeks, as compared to placebo, cilostazol 100 mg twice daily produced a reduction in triglycerides of 29.3 mg/dL (15%) and an increase in HDL-cholesterol of 4.0 mg/dL. Cilostazol affects both vascular beds and cardiovascular function. It produces non-homogeneous dilation of vascular beds, with greater dilation in femoral beds than in vertebral, carotid or superior mesenteric arteries. Renal arteries were not responsive to the effects of cilostazol.

Pharmacokinetics:
Absorption: Cilostazol is absorbed after oral administration. A high fat meal increases absorption, with an approximately 90% increase in Cmax and a 25% increase in AUC. Absolute bioavailability is not known. Cilostazol is extensively metabolized by hepatic cytochrome P-450 enzymes, mainly 3A4, and, to a lesser extent, 2C19, with metabolites largely excreted in urine. Two metabolites are active, with one metabolite appearing to account for at least 50% of the pharmacologic (PDE III inhibition) activity after administration of cilostazol. Pharmacokinetics are approximately dose proportional. Cilostazol and its active metabolites have apparent elimination half-lives of about 11 to 13 hours. Cilostazol and its active metabolites accumulate about 2-fold with chronic administration and reach steady state blood levels within a few days. The pharmacokinetics of cilostazol and its two major active metabolites were similar in healthy subjects and patients with intermittent claudication due to peripheral arterial disease
Distribution: Plasma Protein and Erythrocyte Binding: Cilostazol is 95 to 98% protein bound, predominantly to albumin. The mean percent binding for 3,4-dehydro-cilostazol is 97.4% and for 4´-trans-hydroxy-cilostazol is 66%. Mild hepatic impairment did not affect protein binding. The free fraction of cilostazol was 27% higher in subjects with renal impairment than in healthy subjects. The displacement of cilostazol from plasma proteins by erythromycin, quinidine, warfarin, and omeprazole was not clinically significant.
Metabolism: Cilostazol is eliminated predominately by metabolism and subsequent urinary excretion of metabolites. Based on in vitro studies, the primary isoenzymes involved in cilostazol metabolism are CYP3A4 and, to a lesser extent, CYP2C19. The enzyme responsible for metabolism of 3,4-dehydro-cilostazol, the most active of the metabolites, is unknown.
Elimination: Following oral administration of 100 mg radiolabeled cilostazol, 56% of the total radioactivity AUC in plasma was cilostazol, 15% was 3,4-dehydro-cilostazol (4-7 times as active as cilostazol), and 4% was 4´-trans-hydroxy-cilostazol (one fifth as active as cilostazol). The primary route of elimination was via the urine (74%), with the remainder excreted in feces (20%). No measurable amount of unchanged cilostazol was excreted in the urine, and less than 2% of the dose was excreted as 3,4-dehydro-cilostazol. About 30% of the dose was excreted in urine as 4´-trans-hydroxy-cilostazol. The remainder was excreted as other metabolites, none of which exceeded 5%. There was no evidence of induction of hepatic micro enzymes.

Indication:
Cilostazol 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 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.

Recommended Dose:
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 (Cmax) 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. 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.
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.

Mode of Administration:
Orally

Contraindication:
- 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] hemorrhagic stroke, proliferative diabetic retinopathy, poorly controlled hypertension)
- Patients with any history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopic, 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.

Warnings and Precautions:
The suitability of treatment with cilostazol should be carefully considered alongside other treatment options such as revascularization.
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 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.
Due to cilostazol 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. Caution is needed when co-administering cilostazol with any other agent who has the potential to reduce blood pressure due to the possibility that there may be an additive hypotensive effect with a reflex tachycardia. Caution should be exercised when co-administering cilostazol with any other agents that inhibit platelet aggregation.

Interactions with Other Medicaments:
Inhibitors of platelet aggregation
Cilostazol is a PDE III inhibitor with antiplatelet activity. In a clinical study in

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Size: 170 x 240 mm

healthy subjects, cilostazol given 150 mg two times a day 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 hemorrhagic 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 thromboplastic 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.
A higher rate of hemorrhage 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.
Other potential interactions
Caution is needed when co-administering cilostazol with any other agent who has the potential to reduce blood pressure due to the possibility that there may be an additive hypotensive effect with a reflex tachycardia.

Pregnancy and Lactation:
Pregnancy:
There are no adequate data in the use of cilostazol in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Cilostazol must 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 Cilostazol is not recommended during breast feeding.
Fertility:
Cilostazol did not alter fertility in animal studies.

Undesirable Effect:

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 extra systoles
	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

Overdose and treatment:
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.

Storage Condition:
Store at temperatures not exceeding 30°C.

Dosage Forms and packaging available:
Cilostazol (Cilozol-50) Tablet USP 50 mg packed in
Alu/Alu Blister pack of 3X10's (Box of 30's)
Cilostazol (Cilozol-100) Tablet USP 100 mg packed in
Alu/Alu Blister pack of 3X10's (Box of 30's)

ADR REPORTING STATEMENT:
"FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph
Seek medical attention immediately at the first sigh of Adverse Drug Reaction.

Date of Revision of Package Insert:
June 2020

Manufactured by :
MICRO LABS LIMITED
92, Sipcot Industrial Complex,
Hosur-635 126, India

Imported and Distributed by:
BROWN & BURK PHaILIPPINES INC.
U-501, 5/F SEDCCO 1 Bldg., 120 Rada cor.
Legaspi Sts., Legaspi Village, Makati City, Philippines

EXG-ML01I-1651

MICRO LABS LIMITED, BANGALORE, INDIA			
1	Product Name	Cilozol-50/100	Colours Used
2	Strength	50 mg & 100 mg	
3	Component	Leaflet	BLACK
4	Category	Export - Philippines	
5	Dimension	170 x 240 mm	
6	Artwork Code	EXG-ML01I-1651	
7	Pharma Code	N/A	
8	Reason for Change	New Artwork	

	Prepared by (DTP)	Checked by (PD)	Approved by			
			Head CQA	Head Production/ Packing (Site)	Head QC (Site)	Head QA (Site)
Sign	Kantharaju L.					
Date	05-06-2020					