

NEW DRUG EVALUATION

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CILOSTAZOL

Cilostazol is an antiplatelet agent licensed for treating peripheral arterial disease. It increases walking and claudication distance and improves functional status. Although efficacy is superior to that of pentoxifylline, it has not been compared directly with naftidrofuryl. Cilostazol decreases triglycerides and increases HDL-cholesterol levels but the clinical importance of this is unknown. Common adverse effects include headache and gastrointestinal disturbances. The place of cilostazol in therapy has not yet been adequately defined.

What is it?

Cilostazol is an antiplatelet agent licensed as treatment to improve walking distance in patients with intermittent claudication who do not have rest pain or evidence of peripheral tissue necrosis. The recommended dose is 100 mg twice daily, taken 30 minutes before or 2 hours after meals. Cilostazol inhibits platelet aggregation by inhibiting platelet phosphodiesterase type III. It also has vasodilator activity but the importance of this has not been determined. In patients with intermittent claudication without hypercholesterolaemia (approximate mean LDL-cholesterol 3.6 mmol/l), cilostazol reduced plasma triglycerides by 15%, increased HDL-cholesterol by 10% and had no effect on LDL- or total cholesterol¹.

How effective is it?

Cilostazol has been compared with placebo in several double-blind randomised trials conducted over 12 - 24 weeks in 1230 patients with peripheral arterial disease²⁻⁵. The mean ages of patients ranged from 63 - 67 yr; approximately 35% - 50% were current smokers and 20% - 30% had diabetes. All trials excluded the use of other antiplatelet agents. However in a further study, concurrent use of low-dose aspirin did not appear to alter the effects of cilostazol on walking distance and the onset of pain⁶.

Total walking distance, a primary endpoint in all 4 studies, ranged from 120 m to 240 m at baseline; this was significantly increased with cilostazol (by 76 to 129m) compared with placebo (-17 to 37m)²⁻⁵. Cilostazol also significantly increased the distance walked before onset of pain (initial claudication distance)^{2,4} and improved functional status (measured using the SF-36 questionnaire and disease-specific questionnaires) compared with placebo^{2,3}.

Cilostazol has been compared with pentoxifylline 400 mg *tds* and placebo in 699 patients with peripheral arterial disease⁶. The mean age was 66; the prevalence of smoking was 35% and 30% had diabetes. The use of aspirin and other NSAIDs was permitted. At baseline, mean total walking distance was approximately 240 m. After 24 weeks, cilostazol was associated with a significantly greater increase (107 m) than pentoxifylline (64 m) or placebo (65 m). Cilostazol also increased initial claudication distance significantly more than pentoxifylline but there was no difference between the drugs in their effects on functional status.

How safe is it?

An analysis of data pooled from clinical trials involving 2702 patients included 998 patients treated with cilostazol 100 mg *bd*. Of these, 16% discontinued cilostazol due to adverse effects compared with 9% taking placebo and 21% taking pentoxifylline. Adverse events occurring more frequently with cilostazol than placebo were headache (33% vs. 13%), diarrhoea (19% vs. 6.7%), abnormal stools (15% vs. 4.1%), palpitations (10% vs. 1.0%) and tachycardia (4.3% vs. 0.7%).

What other options are there?

The National Service Framework for Coronary Heart Disease states that patients with peripheral arterial disease should take low-dose aspirin as prophylaxis against cardiovascular events and a statin if cholesterol is raised. They should also receive advice on stopping smoking and changing lifestyle to reduce other modifiable risk factors⁸. Exercise increases total walking distance and duration^{9,10}; overall, naftidrofuryl increases total walking distance by 28 - 130 m more than placebo in patients capable of walking approximately 325 m at baseline⁹. The Joint Formulary Committee of the BNF

classifies other drugs (moxisylyte, nicotinic acid derivatives, pentoxifylline and cinnarizine) as less suitable for prescribing.

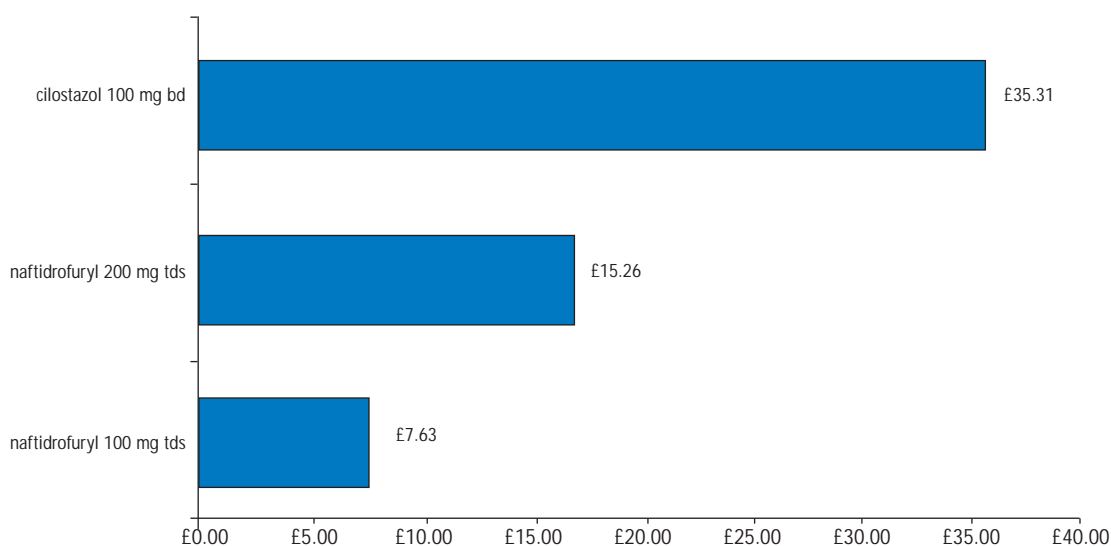
When should it be used?

The available evidence does not clearly define the place of cilostazol in the management of patients with peripheral arterial disease. Although it increases total walking distance by more than pentoxifylline,⁶ it has not been compared directly with naftidrofuryl. It has not been evaluated specifically in patients whose mobility is

limited by pain despite adherence to first-line strategies such as lifestyle changes and exercise training.

A therapeutic trial of cilostazol should be reserved for patients who have incapacitating intermittent claudication unresponsive to alternative agents. It should only be continued if an objective benefit is obtained. No dose adjustment is necessary for elderly patients. Cilostazol is contraindicated in patients with heart failure, and those with any known predisposition to bleeding.

How much does it cost?



Cost for 28 days treatment (prices from MIMS January 2003)

NB Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, A-abstract, E-editorial

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