Scottish Medicines Consortium

Re-Submission

cilostazol 100mg tablets (Pletal®) **No. (86/04)**

Otsuka

4 October 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

Cilostazol (Pletal®) is not recommended for use within NHS Scotland for 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.

Although in clinical trials, cilostazol improved pain-free and maximal-walking distances and had limited effects on quality of life assessments of physical function and pain, its efficacy and safety profile in Scottish patients, who are concomitantly treated with an antiplatelet drug, is unclear. The clinical effectiveness and cost-effectiveness were not demonstrated.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

cilostazol 100mg tablets (Pletal®)

Licensed indication under review

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.

Dosing information under review

100mg twice a day

UK launch date

June 2002

Comparator medications

Naftidrofuryl oxalate, inositol nicotinate, oxpentifylline and cinnarizine are licensed in the UK for treatment of intermittent claudication. However, the latter three are designated "less suitable for prescribing" by the British National Formulary (BNF) Joint Formulary Committee. The Scottish Intercollegiate Guidelines Network (SIGN) notes that naftidrofuryl may improve symptoms of patients suffering moderate disease (claudication distance <500m) but its effect on disease outcome is unknown. SIGN does not recommend any of the other drugs.

Cost per treatment period and relevant comparators

Drug	Dose range	Annual cost (£)*
Cilostazol	**100mg twice daily**	**460**
Inositol nicotinate	1500mg twice or 1000mg three times daily	444-449
Oxpentifylline	400mg two to three times daily	166-249
Naftidrofuryl oxalate	100-200mg three times daily	101-201
Cinnarizine	75mg two to three times daily	38-57

*costs from eVadis drug dictionary, accessed in June 2005.

Summary of evidence on comparative efficacy

Cilostazol is a peripheral vasodilator. The exact mechanism by which it improves blood flow to the extremities is not fully understood, but is thought to be multifactorial, as cilostazol is a phosphodiesterase inhibitor with antiplatelet and vasodilatory effects.

Two 24-week double-blind trials recruited patients aged at least 40 years with moderate-to-severe intermittent claudication secondary to peripheral vascular disease for at least six months, which had been stable for at least three months. In the UK study patients had a pain-free walking distance (PFWD) and a maximal walking distance (MWD) of ≥30m and ≤450m, respectively, on a constant load treadmill test (3.2km/hour on a 10% incline) and in the American study patients had PFWD and MWD of ≥54m and ≤540m on a variable load treadmill test (3.2 km/hour with incline increasing by 3.5% every 3 minutes). In the respective studies 370 and 698 patients were randomised to placebo, cilostazol 100mg twice daily or oxpentifylline 400mg three times a day. The primary outcome, MWD on treadmill test was log transformed and then assessed via analysis of covariance (ANCOVA) in patients with at least

one post-baseline observation using last observation carried forward (LOCF) for missing data. In the American study cilostazol 100mg significantly increased, compared to placebo and to oxpentifylline, MWD (on variable load treadmill test) from baseline to endpoint. In the respective groups median increases in MWD were 63m, 39m and 31m. In the UK study, there were no significant differences between cilostazol and placebo or oxpentifylline in MWD (on constant load treadmill test) change from baseline to endpoint. In the respective groups median increases in MWD were 31m, 23m and 29m.

As noted previously, oxpentifylline is designated as "less suitable for prescribing" by the BNF Joint Formulary Committee. The new economic model with this resubmission assumes that many patients receive no treatment and thus includes placebo as comparator. Details of placebo-controlled trials are provided below.

Six double-blind trials recruited patients aged at least 40 years with moderate-to-severe intermittent claudication secondary to peripheral vascular disease for at least six months, which had been stable for at least three months. Patients had PFWD 30-200m and generally had MWD ≤320m on constant load treadmill tests (3.2 km/hour on a 12.5% incline), except for two studies where patients had PFWD ≥54m and MWD ≤805m on variable load treadmill test (3.2km/hour with incline increasing by 3.5% every 3 minutes). Patients were randomised to cilostazol 100mg twice daily or placebo for 12, 16 or 24 weeks. Three studies included additional cilostazol treatment groups, 50mg in two studies and 150mg in one study. Results for the groups receiving the licensed dose, 100mg twice daily, are detailed in the table below. The primary outcome, geometric percent mean change from baseline to endpoint in MWD, was compared via ANCOVA in intention-to-treat populations with LOCF. Improvement in MWD from baseline to endpoint was significantly greater with cilostazol 100mg twice daily compared to placebo in all but one of the trials. In the trials where significant differences were observed, MWD increased from baseline with cilostazol by about 37% to 51% and 28% to 38% on constant and variable load treadmill tests, respectively, compared with placebo increases of –3% to 15% and 5% to 10%, respectively. Median increases in MWD with cilostazol were 24-35m and 59-70m on the respective tests and with placebo were -2-10m and 9-28m. These results are summarised in the table below.

Median baseline, median and geometric mean percent change in maximal walking distance in patients with intermittent claudication.

Study duration			Maximal walking distance (meters)					
	N		Median baseline		Mean % change*		Median change	
	CLZ	placebo	CLZ	placebo	CLZ	placebo	CLZ	placebo
24 weeks[B]	175	170	114	108	51	15	34.5	9
24 weeks[B]	133	129	109	104	37	12	27.5	10
12 weeks[B]	54	27	100	108	40	-3	24.5	-2
12 weeks[B]	72	70	114	106	23[#]	22	16.5	23
16 weeks[A]	119	120	188	191	38	5	70.5	9
12 weeks[A]	95	94			28	10	58.5	28

* geometric mean percent change = 100 x (geometric mean change ratio –1); geometric mean change ratio = exp (Σ log (endpoint MWD / baseline MWD)$_{1\text{-}n}$ / n); CLZ = cilostazol 100mg twice daily; A = walking distance assessed on variable treadmill test (3.2 km/hour, increasing incline 3.5% per 3 minutes); B = walking distance assessed on constant load treadmill test (3.2km/hour, 12.5% incline); # difference versus placebo not significant

A meta-analysis pooled data from 1751 patients with baseline and at least one post-baseline measure, using LOCF for missing data, in the trials detailed above, excluding the smallest placebo-controlled trial and the comparison to oxpentifylline conducted in the UK. This found mean walking impairment questionnaire (WIQ) scores increased from baseline by 11, 8, 6 and 15 points on 100-point scales for walking distance, walking speed, stair-climbing and pain

severity with cilostazol 100mg twice daily. These were significantly greater than mean increases with placebo: 6, 3, 2 and 9, respectively. Mean physical summary score on the short-form 36 (SF-36) quality of life questionnaire increased with cilostazol 100mg twice daily from 36 at baseline to 38, an absolute change of 2 points on a 100-point scale and a change relative to baseline of 5%. Changes in the three subscales, which contribute to the SF-36 physical summary score (physical functioning, role limitation-physical and bodily pain), were significantly greater than improvements with placebo, with mean percent changes relative to baseline with cilostazol 100mg twice daily of 9%, 6% and 7%, respectively. The clinical significance of these effects is unknown.

SF-36 quality of life data from the two 24-week placebo-controlled trials of cilostazol were used in the economic model provided with this submission. In the first study, mean change from baseline to 24 weeks for SF-36 physical function and bodily pain were significantly improved with cilostazol 100mg twice daily (7.1 and 7.2 points, respectively) compared to placebo (2.0 and -1.8 points, respectively) in patients with at least one post-baseline measure. Limited details of an analysis in the second study indicate improvement in SF-36 physical function with cilostazol 100mg twice daily compared with placebo of borderline significance (p=0.048).

Summary of evidence on comparative safety

The most common adverse effects in the cilostazol clinical trials were headache (>30%) and symptoms of gastro-intestinal upset, such as diarrhoea or abnormal stools (>15%), which were usually of mild to moderate severity and sometimes alleviated by dose reductions. Adverse cardiovascular effects were also common and included dizziness, oedema, palpitations, tachycardia, angina pectoris, arrhythmias and ventricular extrasystoles.

Except for the American comparison with oxpentifylline, which allowed patients to receive aspirin up to 81mg daily, all phase 3 trials excluded patients taking antiplatelet doses of aspirin. Thus data are limited on the safety of cilostazol, which has antiplatelet effects, in combination with antiplatelet doses of aspirin. The summary of product characteristics for cilostazol advises caution when co-administering drugs which inhibit platelet aggregation, such as low-dose aspirin and clopidogrel. If co-administration is undertaken, consideration should be given to monitoring bleeding time and it is recommended that the dose of aspirin should not exceed 80mg daily. It also contra-indicates use in patients with a predisposition to bleeding.

Summary of clinical effectiveness issues

SIGN guidelines on drug therapy of peripheral vascular disease recommend that patients with intermittent claudication should receive aspirin 75-300mg daily as prophylaxis against cardiovascular effects. This low-dose aspirin has antiplatelet effects and could potentially interact with cilostazol, which also has antiplatelet effects.

Given that there is evidence, if limited, that antiplatelet agents may improve walking distance in claudication by a degree similar to that produced by cilostazol, it is possible that the full benefits of cilostazol will not be realized in Scottish patients. There are also limited trial and long-term safety data relating to the concomitant administration of these two drugs. Thus, in practice, both the efficacy and safety of this combination is unknown.

Summary of comparative health economic evidence

The manufacturer submitted a decision tree model comparing cilostazol to placebo over a 24-week period. The two main data sources were clinical trials for effectiveness and utilities and 11 vascular surgeons and 4 GPs for resource use.

The incremental cost per patient is about £200 (primarily drug costs) and the estimated QALY gain is 0.016, giving an incremental cost effectiveness ratio of about £12,700 per QALY. Sensitivity analyses suggest the cost per QALY is likely to be under £15,000, assuming use is limited to 24 weeks and there are no adverse effects.

The comparator, the model structure and resource use inputs seem relevant to the Scottish setting. However, clinical experts advised that the duration of treatment is likely to exceed 24 weeks in many patients and could be life-long. In addition, virtually all eligible patients will be taking aspirin, which may affect both the efficacy and safety of cilostazol treatment. The cost-effectiveness of the drug is therefore not demonstrated.

Budget impact

The manufacturer estimated patient numbers, increase in drugs costs and healthcare costs for years 1 and 5 based on patients using the drug for 24 weeks per annum. This treatment duration may not be realistic. If patients are prescribed the drug for considerably longer durations then annual costs for 730 patients in year 1 and 1200 patients in year 5 would double to over £400 per patient, equivalent to a budget impact of about £293,000 in year 1, rising to £480,000 in year 5.

Guidelines and protocols

The 1998 SIGN publication number 27, *drug therapy for peripheral vascular disease* recommends that all patients with intermittent claudication should receive aspirin 75mg to 300mg daily as long-term prophylaxis against cardiovascular events, and in those who have undergone angioplasty or surgical graft therapy for peripheral vascular disease, as prophylaxis against re-stenosis and graft failure. It is also noted that naftidrofuryl 200mg three times daily may improve the symptoms of patients suffering moderate disease (claudication distance <500m) but its effect on disease outcome is unknown. Inositol nicotinate is not recommended and there was insufficient evidence to make a recommendation about the use of oxpentifylline or cinnarizine in the treatment of intermittent claudication. This guideline is currently under review.

Additional information

After consideration of a full submission, the Scottish Medicines Consortium issued advice in February 2004 that cilostazol was not recommended within NHS Scotland for the treatment of intermittent claudication. It improves maximal and pain-free walking distances more than placebo, but has limited effects on quality of life assessments. There are concerns about clinical effectiveness, including potential for several major drug interactions including with antiplatelet therapy which is recommended by SIGN for patients with peripheral vascular disease. The economic case for this product has not been proven and it is substantially more expensive than its competitors.

Advice context:
No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 15 July, 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

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Food and Drug Administration. Medical review of Pletal. www.fda.gov/cder/foi/nda/99/20863.htm

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