PUBLIC SUMMARY DOCUMENT
Product: Cilostazol, tablets, 50 mg and 100 mg, Pletal®
Sponsor: PharmaLink Pty Ltd
Date of PBAC Consideration: July 2009

1. Purpose of Application

To request an Authority Required listing for improvement of intermittent claudication as indicated by increased maximal and pain-free walking distances in patients who do not have rest pain and who do not have evidence of peripheral tissue necrosis.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration status

Cilostazol was TGA registered on 29 January 2009 for the symptomatic improvement of intermittent claudication as indicated by increased maximal and pain-free walking distances, in patients who do not have rest pain and who do not have evidence of peripheral tissue necrosis.

4. Listing Requested and PBAC's View

Authority Required

Symptomatic improvement of intermittent claudication as indicated by increased maximal and pain-free walking distances in patients who do not have rest pain and who do not have evidence of peripheral tissue necrosis.

See Recommendation and Reasons for PBAC's view.

5. Clinical place for the proposed therapy

Cilostazol is a pharmacological alternative to medical treatment options (supervised exercise programs, angioplasty or bypass surgery) and if PBS-listed, would provide a treatment option for the symptoms of intermittent claudication (IC).

6. Comparator

The submission nominated placebo, for standard medical management as the main comparator. The PBAC considered the main comparator appropriate.

7. Clinical trials

The submission presented a meta-analysis of 10 randomised controlled trials, of either 12, 16 or 24 weeks duration, comparing cilostazol 100 mg and 50 mg tablets with placebo and one 3 year randomised controlled trial to assess morbidity and mortality compared to placebo. Seven trials used constant load treadmills and three used variable load (stepped) treadmills to assess walking distance. Three trials included pentoxifylline 400 mg in comparison to cilostazol 100 mg and placebo.

Details of the published randomised trials presented are shown in the following table.

Trial ID	Protocol title/ Publication title	Publication citation
21.90.201 Dawson 1998	Dawson DL. Cutler BS. Meissner MH. Strandness DE Jr. *Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial*.	Circulation.1998 98(7):678-86
21.92.202 Beebe 1999	Beebe HG. Dawson DL. Cutler BS. Herd JA. Strandness DE Jr. Bortey EB. Forbes WP. *A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial.*	Archives of Internal Medicine. 1999 159(17):2041-50
21.93.201 Elam 1998	Elam MB. Heckman J. Crouse JR. Hunninghake DB. Herd JA. Davidson M. Gordon IL. Bortey EB. Forbes WP. *Effect of the novel antiplatelet agent cilostazol on plasma lipoproteins in patients with intermittent claudication.*	Arteriosclerosis, Thrombosis & Vascular Biology. 1998 18(12):1942-7
21.94.201 Strandness 2002	Strandness DE Jr. Dalman RL. Panian S. Rendell MS. Comp PC. Zhang P. Forbes WP. *Effect of cilostazol in patients with intermittent claudication: a randomized, double-blind, placebo-controlled study.*	Vascular & Endovascular Surgery. 2002 36(2):83-91
21.94.203 Money 1998	Money SR. Herd JA. Isaacsohn JL. Davidson M. Cutler B. Heckman J. Forbes WP. *Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease.*	Journal of Vascular Surgery. 1998 27(2):267-74; discussion 274-5
21.96.202 Dawson 2000	Dawson DL. Cutler BS. Hiatt WR. Hobson RW 2nd. Martin JD. Bortey EB. Forbes WP. Strandness DE Jr. *A comparison of cilostazol and oxpentifylline for treating intermittent claudication.*	American Journal of Medicine. 2000 109(7):523-30
21.98.214 CASTLE	Hiatt WR, Money, SM, Brass EP *Long-term safety of cilostazol in patients with peripheral artery disease: The CASTLE study (Cilostazol: A Study in Long-term Effects).* Stone, WM, Demaerschalk, BM, Fowl, RJ and Money, SR. *Type 3 Phosphodiesterase Inhibitors May Be Protective Against Cerebrovascular Events in Patients with Claudication.*	J Vascular Surgery, 47(2):330-336 Journal of Stroke and Cerebrovascular Diseases, 2008: 17(3) 129-133

8. Results of trials

The primary outcome was Actual Claudication Distance (ACD), reported as weighted mean absolute change from baseline in metres walked, weighted mean percentage change from baseline of metres walked and Ln (distance walked at endpoint/distance walked at baseline) at 12 weeks, 24 weeks and endpoint intervals for variable load, constant load and combined treadmill data sets. Similar measures of the key secondary outcome of Initial Claudication Distance (ICD) were also presented. The patients enrolled in the clinical trials were generally representative of the Australian population likely to be treated.

The baseline walking distances for the patient populations showed substantive heterogeneity across the trials in the distance walked at baseline, large changes in the placebo arm as well as heterogeneity in the size of the treatment effect.

There were statistically significant differences in the ratio of geometric mean, change in distance walked and % change in distance walked for all ACD and ICD analyses for cilostazol 100 mg versus placebo.

The key outcomes used in the economic evaluation were the absolute change in ACD and the absolute change in ICD from baseline in metres walked at 24 weeks following cilostazol 100 mg twice daily. For these outcomes, the average change in ACD was 40.60 metres (95%CI: 12.71, 68.49), and average change in ICD was 24.31 metres (95% CI: 8.48, 40.15).

While there was a statistically significant improvement in mean ACD and ICD (change from baseline at 24 weeks) for cilostazol 50mg versus placebo in trial 21.92.202, there was no statistically significant difference between cilostazol 50mg and placebo in ACD and ICD in trial 21.94.201.

The results of the meta-analyses of the quality of life results (Medical Outcomes Scale SF-36) from 7 trials showed statistically significant differences in the mean change from baseline score in favour of cilostazol 100 mg in 3 of 8 health concepts; Bodily Pain, Physical Function and Role Limitations due to Physical Health.

The incidence of serious adverse events (SAEs) was low and comparable between cilostazol 100 mg and placebo trial arms. The most frequent reported SAEs were cardiac disorders (13.3% of patients) and vascular disorders (10.6% of patients) which may be related to the underlying clinical condition. Cilostazol is contraindicated in patients with heart failure. Headache, dizziness, pain, diarrhoea, abnormal stools, peripheral oedema and palpitations were the most commonly reported adverse events, and were statistically significantly more likely in the cilostazol treated patients compared to placebo.

The safety profile of cilostazol 100mg in the three year CASTLE trial was consistent with the safety profile established in the shorter clinical trials. There was no increase in incidence or severity of adverse events, no differences between the cilostazol and placebo in cardiovascular morbidity and mortality and no differences between the cilostazol and placebo and adverse events related to bleeding (with or without concomitant clopidogrel, aspirin or both).

9. Clinical Claim

The submission described cilostazol as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo.

For PBAC's views see Recommendation and Reasons.

10. Economic analysis

The submission presented a trial-based economic evaluation. The incremental cost per metre gained in walking distance was calculated from the cost of cilostazol over 24 weeks (168 days) over the mean weighted change from baseline in metres walked. The submission calculated incremental cost effectiveness ratios based on both ACD and ICD

for cilostazol 100 mg. The incremental cost per additional metre walked at 24 weeks in ACD was < $100 and in ICD approximately 67% more that the ACD value.

The Pre-PBAC response provided an indicative incremental cost-effectiveness ratio (ICER) of < $15,000 per QALY gained based on a utility gain calculated using data from Letterstal et al (2008).

For PBAC's views see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications:

The estimated financial cost per year to the PBS was < $10 million in Year 5. The DUSC advised the uptake of cilostazol was uncertain, noting the proportion of eligible patients who may be treated to be very uncertain.

12. Recommendation and Reasons:

The PBAC considered the main comparator, placebo for standard medical management, appropriate, noting however, that the comparative data against pentoxifylline, which is not PBS listed, was also informative.

It was noted that the TASC II Guidelines for the treatment of peripheral arterial disease submitted as the clinical management algorithm for the treatment of intermittent claudication were from an industry supported group including the manufacturer of cilostazol.

The PBAC noted that for the outcome measures of Actual Claudication Distance (ACD) and Initial Claudication Distance (ICD), the meta-analyses showed a statistically significant improvement in both measures for cilostazol 100 mg versus placebo. However, while there was a statistically significant improvement in mean ACD and ICD for cilostazol 50 mg versus placebo in trial 21.92.202, there was no statistically significant difference between cilostazol 50 mg and placebo in ACD and ICD in trial 21.94.201.

The PBAC noted that there was substantial variability in ACD and ICD results within the trials, as well as across the trials, as shown by the heterogeneity in both the baseline and the change from baseline walking distances for the trials included in the meta-analysis. This heterogeneity increased the uncertainty around the pooled estimates for the weighted mean difference in both ACD and ICD. The ICD, a measure of distance before initial claudication pain, was considered to be the more relevant clinical endpoint, and it was noted the meta-analyses showed a gain at the 24 week time point of 24.31 m, compared to a gain of 40.6 m for ACD.

The Pre-PBAC Response advised that the reason for the apparent heterogeneity across the trials in the distance walked at baseline, including changes in the placebo arm as well as in the size of treatment effect was due to two different treadmill protocols. The PBAC acknowledged this point but still considered that it did not deal with the uncertainty about the extent of clinical benefit with cilostazol.

Given that the FDA and the TGA have expressed concerns in relation to drug interactions between cilostazol and other platelet aggregation agents, the PBAC was pleased to note that the safety profile of cilostazol 100 mg in the three year CASTLE trial was consistent

with the safety profile established in the shorter clinical trials. However, the lack of data on drug interactions with other antiplatelet agents was noted.

Based on the clinical data submitted the PBAC accepted that cilostazol 100 mg was superior in comparative effectiveness and inferior in terms of comparative safety to placebo. However, it was uncertain as to the clinical significance of the small walking distances gained in ACD and ICD.

The PBAC did not consider that the primary analysis providing incremental cost-effectiveness in terms of cost per additional metre gained at 24 weeks was informative, given the uncertainty around the clinical benefits gained. It was considered than an ICER expressed in terms of QALY gained, given the availability of SF-36 data at 24 weeks from 7 of the comparative trials would have been more appropriate. The Committee noted with interest that the SF-36 data showed statistically significant differences in favour of cilostazol 100 mg in 3 of 8 health concepts only (bodily pain, physical function and role limitations due to physical health).

The Pre-PBAC response provided an indicative ICER of < $15,000 per QALY gained based on a utility gains calculated using data from Letterstal et al (2008) . However, the PBAC had the several concerns with this calculation. The PBAC considered these concerns cast doubt on the applicability of the utility weights.

The PBAC noted the DUSC advised the estimates of patients treated may be an underestimate, that there is substantial uncertainty in the derivation of the eligible population and the likely treated population owing to limited and poor quality data sources to substantiate the estimate, and that usage may result in net costs > $10 million per year to the PBS.

The PBAC therefore rejected the submission on the basis of uncertain clinical benefit, uncertain cost-effectiveness and uncertain utilisation estimates.

Recommendation
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

PharmaLink is working with PBAC to address the issues.