PUBLIC SUMMARY DOCUMENT
Product: CILOSTAZOL, tablets, 50 mg and 100 mg, Pletal®
Sponsor: PharmaLink Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission sought an Authority Required listing 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.

2. Background

At the July 2009 meeting, the PBAC rejected a submission for cilostazol for an authority required listing for the symptomatic improvement of intermittent claudication on the basis of uncertain clinical benefit, uncertain cost-effectiveness and uncertain utilisation estimates.

Full details in the July 2009 Public Summary Document.

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

Pletal is indicated 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.

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

Intermittent claudication (IC) is a common debilitating symptom of peripheral arterial obstructive disease. IC is characterised by pain in the legs or buttocks that occurs with exercise and which subsides with rest.

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 IC, such as the distance walked before onset of pain. There are no products currently listed on the PBS for the symptomatic treatment of IC.

6. Comparator

As previously, the re-submission appropriately nominated placebo as the main comparator.

7. Clinical Trials

Clinical trials

The re-submission presented a revised meta-analysis of 11 randomised trials comparing cilostazol 100 mg twice daily with placebo, compared with a meta-analysis of 10 randomised trials in the previous submission.

(*Refer to the July 2009 Public Summary Document for details of the published trials presented in the previous submission.)*

The re-submission presented two additional trials, O'Donnell 2009a and O'Donnell 2009b. A comparison of the two publications suggested that the patients reported in O'Donnell (2009b) might have been a subset of the patients reported in O'Donnell (2009a). O'Donnell 2009a was incorporated into the revised meta-analysis in the re-submission.

Details of these trials are in the table below:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
O'Donnell ME et al (2009a)	The effects of cilostazol on exercise-induced ischaemia-reperfusion injury in patients with peripheral arterial disease.	Eur J Vasc Endovasc Surg 2009; 37: 326-335
O'Donnell ME et al (2009b)	The vascular and biochemical effects of cilostazol in patients with peripheral arterial disease.	J Vasc Surg 2009; 49:1226-1234

8. Results of Trials

The re-submission reaffirmed the claim that the treatment benefit with cilostazol is clinically relevant, and presented the following information to support this claim:

- Transformation of treadmill walking distances in all trials to real life flat-ground walking distances.
- Correlation of improvement in walking distances with improvement in QoL (SF-36 and WIQ) outcomes
- An analysis of patient rated treatment success with cilostazol compared with placebo
- Expert opinion (Prof Dawson 2009).

Compared to the previous submission, only one new trial was presented in the re-submission in terms of the key outcome of mean change from baseline Actual Claudication Distance (ACD) (O'Donnell 2009a).

New results in this re-submission, and a comparison with the results of the previous submission, are summarised below.

<u>Revised meta-analyses incorporating one additional trial (O'Donnell 2009a):</u>

- Percentage change in ACD from baseline at 24 weeks: difference (weighted mean difference, WMD) between cilostazol 100 mg and placebo = 23.30% (95% CI 7.44 to 39.17), compared to 21.15% (95% CI 5.69 to 36.61) in the previous submission;
- Percentage change in ICD from baseline at 24 weeks: difference = 25.18% (95% CI 3.18 to 47.19), compared to 26.11% (95% CI 2.12 to 50.10) in the previous submission;

New meta-analyses for change in QoL as measured by the WIQ at 24 weeks:
There was statistically significant difference in three (pain or aching in calves, pain or aching in thighs, weakness in one or both legs) of the eight items under the walking impairment subscale, favouring cilostazol 100 mg over placebo. However, there was no statistically significant difference between cilostazol and placebo in any of the WIQ subscales (walking impairment, walking distance, walking speed, stair climbing) at 24 weeks.

The PBAC noted that no new toxicity data were presented in the re-submission. Adverse events were more common in cilostazol-treated patients. The most frequently reported serious adverse events were cardiac (13.3% of patients) and vascular disorders (10.6% of patients) which may be related to comorbidities. The most common adverse events were headache, dizziness, pain, diarrhoea, abnormal stools, peripheral oedema and palpitations.

For PBAC's view, see Recommendation and Reasons

9. Clinical Claim

The submission claimed that cilostazol is statistically significantly superior to placebo for all primary and secondary endpoints but is associated with greater toxicity. This is consistent with the clinical claim in the previous submission, which was accepted by the PBAC.

Concerns about the clinical relevance of the gains in walking distance were addressed through additional meta-analyses of trial-based WIQ data and transformations of the trial-based treadmill distances to flat ground walking distances.

10. Economic Analysis

The re- submission presented an updated cost-effectiveness evaluation.

The re-submission estimated the incremental cost per additional QALY gained to be between $105,000 and $200,000. This is compared to less than $15,000 in the previous submission.

For PBAC's view, see Recommendation and Reasons

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated by the re-submission to be less than 10,000 in Year 5.

The net financial cost per year to the PBS (excluding co-payments) was estimated by the re-submission to be less than $10 million in Year 5, and lower than the estimate in the previous submission.

The re-submission's estimates were considered uncertain by the PBAC.

12. Recommendation and Reasons

The PBAC noted the Consumer Impact Statement on the impact of intermittent claudication (IC) on daily living prepared by the Consumers Health Forum and that nocturnal cramping was identified as a major issue. Not all patients experienced claudication when walking and in those that did, the impact varied considerably.

The PBAC considered that a stopping rule at 12 weeks was inappropriate, given that the submission and Pre-Sub-Committee Response acknowledged that "the maximal effect of cilostazol is not reached until 24 weeks (or beyond)".

The comparator was placebo which was previously considered by the PBAC in July 2009 to be appropriate. The PBAC has also accepted previously the clinical claim that cilostazol is statistically significantly superior to placebo for all primary and secondary endpoints but is associated with greater toxicity. The PBAC noted that cilostazol has increased toxicity when combined with anti-platelet therapy and with other drugs which inhibit CYP3A4 and CYP2C19.

The PBAC noted the results of a systematic review and meta-analysis of drug therapy for IC (Momsen et al 2009) which suggested that the highest benefit in terms of walking distance is obtained by treating patients with lipid lowering agents. The PBAC considered that as cilostazol is intended to be an add-on therapy to standard medical management (including lipid lowering agents in many patients), the incremental benefit of cilostazol treatment that would be realised in the intended PBS population is uncertain.

The PBAC noted there was a revised meta-analysis of 11 randomised trials comparing cilostazol 100 mg twice daily with placebo and that trial-based treadmill walking distances are transformed to flat ground equivalent walking distances. Also quality of life (QoL) outcomes are assessed by the SF-36 and the Walking Impairment Questionnaire (WIQ). A meta-analysis of the WIQ scores was performed.

The PBAC noted that there were no statistically significant differences between cilostazol and placebo in the pooled analyses of utilities (AQoL or SF-6D) at 24 weeks and there were no QoL data beyond 24 weeks.

The PBAC noted from the submission and the Pre-Sub-Committee Response that patients with IC have poor QoL, and considered that any clinically significant improvement in the symptoms of IC would reasonably be expected to be reflected in improvements in QoL. The PBAC remained concerned that no statistically significant differences in QoL were observed between cilostazol and placebo.

The PBAC considered that the transformation of treadmill walking distance to flat ground equivalent walking distances undertaken to be representative of real life was probably reasonable. However, the clinical significance for treated patients of improvements in walking distance of 40.6m in a treadmill test or 94.61m after conversion to real life remained uncertain as the incremental distance is small, and it remained unclear what impact this improvement would have on a patient's day-to-day quality of life.

The PBAC noted that the sponsor claimed that cost per QALY is not meaningful and could not be reliably estimated. An "attempted cost per QALY" was calculated as being between $105,000 and $200,000, based on a difference of 0.01 in preliminary utility gain. The PBAC considered that methodological and dataset issues precluded derivation of a meaningful QALY and that the attempted cost per QALY is not neither reliable nor informative. Further, the PBAC considered that a cost per metre walked is not an appropriate or informative measure.

The PBAC considered that the estimates of use are very uncertain and small changes in uptake and diagnosis or proportion of non-responding patients not stopping therapy have a substantial effect on the financial costs.

The PBAC therefore rejected the submission on the basis of uncertain clinical benefit and a high and uncertain cost-effectiveness ratio.

The PBAC noted that the submission meets the criteria for an independent review.

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

The sponsor is disappointed that the PBAC has rejected the application for PBS listing of cilostazol for the treatment of Intermittent Claudication, a condition that is underdiagnosed and undertreated.

The inability to show gains in utility with cilostazol treatment is largely a methodological problem and not evidence that there are no clinical benefits. The sponsor believes that when a treatment is as specific and localised as that with cilostazol, the cost per QALY is not the most appropriate measure of its worth.

The PBAC comments that "the highest benefit in terms of walking distance is obtained by treating patients with lipid lowering agents." The sponsor does not accept that this reflects the body of evidence. The efficacy of statins has not been compared head-to head to cilostazol and the data quoted by the PBAC, which was not part of the submission, has not been fully reviewed or substantiated.

Further, the PBAC questions the incremental benefit of cilostazol over statin therapy. The. clinical dataset included a large number of patients in whom incremental benefit was demonstrated with cilostazol over background statin therapy.