Cilostazol for the symptomatic treatment of intermittent claudication secondary to peripheral arterial disease

Comments on the ACD and Evaluation Report submitted to the National Institute for Health and Clinical Excellence (NICE) by Otsuka Pharmaceuticals

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COMMENTS ON THE ACD

- Has all of the relevant evidence been taken into account?

1. The size, quality, consistency and general recognition of cilostazol's clinical data has not been adequately addressed in reaching the guidance. Cilostazol's largest and, with regard to positive efficacy, consistent PAD data base has been well recognised by independent institutions and experts. The American College of Cardiology/American Heart Association, the Transatlantic Intersociety Consensus for Management of PAD (TASC II), the Scottish Intercollegiate Guideline Network (SIGN), the American College of Chest Physicians (ACCP 2008), the German Society for Angiology-Vascular Medicine (DGA 2009) accordingly recommend cilostazol with the highest grade of evidence and, in several cases, as the only option for the symptomatic treatment of PAD.

2. The meta-analysis presented by the Assessment Group comparing the change from baseline in log walking distance compared to placebo does not represent a fair or a scientific valid comparison. The selection of trials for the meta-analysis is rather unbalanced in terms of number of trials (6 for cilostazol versus 1 for naftidrofuryl) as well as the total number of patients (> 1200 in cilostazol versus < 200 in naftidrofuryl, both in placebo controlled trials) included in the comparison. Most importantly, the method of estimating a simple percentage improvement in walking distances across trials using different treadmill protocols and comparing this percentage improvements between different treatments is inappropriate, in particular, in cases where treadmill protocols with constant and variable loads are assessed with the same weight in the meta-analysis.

3. It is not justified to transfer improvement in patients' Quality of Life established under treatment with cilostazol to treatments which share only one of cilostazol's beneficial pharmacological effects for patients suffering from arteriosclerotic diseases and for which similar improvement in QoL has not been established. There is evidence that, due to its diversified pharmacological profile, cilostazol, together with the symptomatic improvement in intermittent claudication, improves several additional cardiovascular risk factors in patients with arteriosclerotic disease.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

1. The Assessment Group may have over-estimated the clinical effectiveness of naftidrofuryl as a result of excluding studies. They may also have underestimated the drug cost used in clinical practice.

2. The long term discontinuation data used is based upon cilostazol data – there is no reason to assume that the rates for naftidrofuryl and pentoxifylline will be the same. These rates should potentially have been varied more widely in sensitivity analysis.
3. The model structure used may underestimate the benefit of cilostazol in terms of discontinuing patients being assigned a placebo utility.
4. The model may more appropriately have been developed with health states related to functional ability, and not health states related to treatments.

- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Considering the many uncertainties and weaknesses in the assessment group report and the decision thus based, excluding cilostazol from the recommendation altogether is not sound. The clinical evidence base, the experience of clinicians and patients thus demand another option for the treatment availability. Many patients benefit from cilostazol treatment and naftidrofuryl will not benefit all, or may be contraindicated in some patients. The overall cost for these treatments to NHS is low and the ACD recommendation is unlikely to have a significant budget impact. Moreover cost should really be an issue once robust clinical equivalence between two therapies is established.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?
- Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?"

COMMENTS ON THE EVALUATION REPORT

Clinical Research

A number of naftidrofuryl studies were excluded by the Assessment Group resulting in a loss of evidence base:

- Maas (1984) was excluded despite appearing to meet the inclusion criteria
- Adhoute (1990) and Moody (1994) were excluded due to un-licenced doses of naftidrofuryl. However it is possible that the excluded formulation may be considered equivalent to the included formulation
- Kriessman (1988) was excluded due to language. Exclusion on the basis of language is not recommended by the Centre for Reviews and Dissemination at the University of York
- Boccalon (2001) was excluded due to inclusion of patients with PAD stage III and language. However, the paper does not appear to contain patients with PAD stage III and exclusion on the basis of language is not recommended

The Assessment Group identified five relevant naftidrofuryl studies from their search: Spengel (2002), Kieffer (2001), Adhoute (1986), Trubestein (1984) and Ruckley (1978).

Results from one study, Kieffer (2001) were used in the mixed treatment meta-analysis and subsequent cost-utility analysis.

In 2008, De Backer conducted a very similar search for clinical data related to naftidrofuryl for a Cochrane Review of naftidrofuryl for intermittent claudication. The systematic review searched for randomised placebo controlled clinical trials of oral naftidrofuryl in patients with intermittent claudication (Fontaine stage II). Cochrane excluded studies that used an obsolete dosage, or included a target population not corresponding to Fontaine stage II.

The Cochrane Review identified seven studies: Adhoute (1986), Adhoute (1990), Boccalon (2001), Kieffer (2001), Kriessman (1988), Maass (1984) and Moody (1994). Only two of these studies were identified by the Assessment Group as relevant: Adhoute (1986) and Kieffer (2001). The other five studies were not included as a result of the search.

Adhoute (1990) and Moody (1994) were excluded by the Assessment Group on the basis that they used an unlicensed indication of naftidrofuryl. Adhoute (1990) was a six month double-blind, placebo-controlled, randomised trial performed in hospital and ambulatory care in France and Moody (1994) was a 24 week double-blind, placebo-controlled, randomised trial performed in a hospital setting.

Both studies randomised patients to naftidrofuryl fumarate 316.5mg twice daily or placebo. Naftidrofuryl fumarate 316.5mg and naftidrofuryl oxalate 300mg may be considered to be equivalent doses (Moody 1994 and Gray 1990). By excluding these studies, additional evidence around the effect of naftidrofuryl may be lost. De Backer (2008) included these studies as relevant naftidrofuryl evidence in the Cochrane Review.

It is particularly important to note that both of these trials were 24 weeks in length and therefore would have been included in the mixed treatment meta-analysis and economic analysis thus increasing the evidence base on which NICE was able to base a decision.

Boccalon (2001) was excluded by the Assessment Group on the basis that the population included some patients with Fontaine stage III and was non-English language. No mention of a patient group at Stage III is given in the published paper. This supports the Cochrane Review decision to include Boccalon (2001) in their analysis based on a matching inclusion criterion of Fontaine stage II.

The paper was also excluded by the Assessment Group on the basis of foreign language. As discussed above this is concerning given the quantity of information that would have been available from the paper. Boccalon (2001) was a 12 month, double-blind, placebo-controlled randomised trial performed in an ambulatory care setting in France and therefore would have represented considerable additional evidence for the effect size of naftidrofuryl versus placebo.

With regards to cilostazol, all nine double-blind placebo controlled Phase III/IV trials were performed according to the ‘Note for Guidance on Investigation of Medicinal Products for the treatment of PAD (CPMP/EWP/714/98 rev 1, CPMP 2002) despite several of the trials having been performed prior to issue of the Guidelines. Overall, more than 3070 evaluable patients with PAD were randomised in the trials. In all nine trials prolongation of the Maximal Walking Distance was consistently greater in patients treated with cilostazol, in six

of the nine trials the treatment effect was statistically significant better as compared to placebo. In addition, this positive treatment effect of cilostazol could be shown for all subpopulations (smokers, diabetes mellitus, duration of disease, gender, age, expected co-medication). Cilostazol also showed positive effects on the plasma lipids (HDL-increase, cholesterol and triglyceride decrease) and improvement in the Quality of Life of patients (see Pande, 2010, for a meta-analysis across all nine trials). All eight Phase III trials were part of the original MRP dossier in the UK and all nine Phase III/IV trials were part of the MRP dossier for approval in Germany, Sweden, France and Spain and, as such, were evaluated by several European Health Authorities. A comparable clinical data base for other products for the symptomatic treatment of PAD in size, quality and in particular consistency with respect to clinical efficacy has not been established.

Maximal walking distance (MWD)

No direct RCT to compare the efficacy between both products is available, the Assessment Group conducted a meta-analysis across trials in which the increase in log mean walking distance over placebo has been used for indirect comparison between treatments and was reported highest for naftidrofuryl (60.0%), followed by cilostazol (24.6%) and pentoxifylline (26.4%). This meta-analysis and the resulting overall percentage increases across trials, however, raise several issues which are discussed below.

Six of the eight cilostazol Phase III trials performed qualified for inclusion into the meta-analysis (others were of shorter duration) whereas only a single trial with naftidrofuryl fulfilled the selection criteria. All other (published/reported) naftidrofuryl trials were excluded (lack of endpoints, too short duration, results not reported, inappropriate dosing). Unfortunately, the largest naftidrofuryl trial did not meet the inclusion criteria and the single naftidrofuryl trial selected was one with a placebo effect (29 m improvement in MWD) at the very low end of the scale when taking into consideration the highly heterogeneous placebo treatment effects across published PAD trials.

The Assessment Group included only one study of naftidrofuryl versus placebo, Kieffer (2001) to estimate MWD. They omitted the 24 week studies that had been excluded from the clinical literature search; Adhoute (1990) and Moody (1994), as well as a 24 week study that had been included by the Assessment Group in the clinical literature search, Adhoute (1986), due to lack of data on MWD. Some data on MWD was available from de Backer (2008). Whilst in some studies the endpoint had not been measured, because the Review team had obtained patient level data, they were able to estimate the relative improvement in walking distance on a sub-set of patients.

The included study provided Maximal Walking Distance (MWD) for naftidrofuryl versus placebo that appears to be larger than the estimated for the excluded studies, resulting in an overestimate of naftidrofuryl clinical and cost-effectiveness:

- The estimate of naftidrofuryl MWD used in the economic model is based upon data from Kieffer (2001)
- The data in Kieffer (2001) appears to show a larger treatment effect of naftidrofuryl versus placebo compared with the excluded 24 week studies (Adhoute 1990, Moody 1994)

- Although Adhoute (1986) was included by the Assessment Group in the clinical search, data from this study was not incorporated into the economic evaluation. The relative treatment effect estimated in the Cochrane Systematic Review for Adhoute (1986) is smaller than in Kieffer (2001)
- Consequently, the relative clinical effect of naftidrofuryl may be over-estimated and may result in incorrect estimates of cost-effectiveness

De Backer (2008) estimated the following relative improvement in walking distance for Kieffer (2001), Adhoute (1986), Adhoute (1990) and Moody (1994) for studies reporting final data point at 24 weeks:

Relative Improvement in Maximal Walking Distance by study and by treatment

Study	**Placebo**	**Naftidrofuryl**	**Naftidrofuryl relative improvement – Placebo relative improvement (for illustration)**
Adhoute (1986)	1.316 (1, 1.739)	1.6 (1.036, 2.069)	0.284
Adhoute (1990)	1.176 (1, 1.429)	1.5 (1.167, 2)	0.324
Moody (1994)	1.16 (0.713, 1.665)	1.639 (1, 1.841)	0.479
Kieffer (2001)	1.135 (0.946, 1.419)	1.801 (1.414, 2.248)	0.666

* Modified from de Backer et al (2008)

The Assessment Group included Adhoute (1986) in their clinical literature search. From the table above, it can be shown that the relative treatment effect of naftidrofuryl versus placebo in Adhoute (1986) is lower than in Kieffer (2001). In addition, treatment effect of naftidrofuryl versus placebo in both Adhoute (1990) and Moody (1994) are also lower than Kieffer (2001). As such it is possible that by including only Kieffer (2001) in the meta-analysis and economic evaluation, that the Assessment Group are have over-estimated the clinical and cost-effectiveness of naftidrofuryl.

The calculation of an overall effect (absolute or percentage improvements in maximal walking distances) for a treatment across trials using different treadmill protocols leads to misinterpretation of the real overall outcomes achieved, in particular, if walking distances on constant loads are used with the same weight in the meta-analysis as walking distances on variable loads.

Various treadmill protocols were used during the cilostazol Phase III/IV development; trial protocols with constant load (12.5% and 10%) as well as with variable load (increase of load by 3% every 3 minutes) were used. For variable load treadmill exercise an improvement in walking distance compared to baseline or placebo may result not only in a longer walking time but also in walking longer on a higher treadmill grade (as compared to baseline or placebo). In such cases a simple comparison of absolute walking distances (also when log transformed) is not fair as the comparison does not account for walking on a higher grade compared to baseline and/or to placebo control. One option for a fair comparison in such cases such would be to transform all MWD measured during different treadmill protocols into MWD that would have been achieved under the same conditions, for example via the oxygen consumption on various treadmill grades.

Discontinuations (long term)

Long term discontinuation rates were taken from the only long term study by Hiatt (2008); a cilostazol study (68% patients discontinue by 36 month) and the Assessment Group assumed discontinuations are the same as cilostazol for all other therapies. However there are two reasons why this assumption and use of the data may not be appropriate:

- In the model, patients discontinuing drug therapy are moved to the "No vasoactive drug treatment" health state where they are assigned a quality of life associated with placebo walking distance. This is not appropriate for many of the discontinuations particularly after 24 weeks.
- An assumption that discontinuation rates are the same across therapies may not be appropriate. There is no reason to suggest that the discontinuation rates in the long term are the same as cilostazol for naftidrofuryl or pentoxifylline.

Cilostazol is the only therapy with a long-term safety study (Hiatt, 2008). This study demonstrated that there was no increase in risk for all-cause or cardiovascular mortality between the cilostazol and placebo groups during any time-point of the study, there was no increase in the incidence or severity of AEs after long-term exposure and there was no evidence of increased bleeding risks associated with cilostazol in comparison with placebo, even in patients taking background aspirin or anticoagulant.

Due to a lack of long term data from naftidrofuryl or pentoxifylline, the Assessment Group was not able to model long term effects. There is therefore uncertainty in the model results as any long term effects could impact upon the cost-effectiveness figure. The Assessment Group acknowledge this as a limitation of the analysis.

Health-related Quality of Life

The Assessment Group estimated a linear regression based upon MWD and utility (as measured by the SF-6D). The sample size used to estimate utility data was small (n=109) and the results are subject to uncertainty. It is also unclear whether the Assessment Group considered and assessed alternative model specifications. Moreover it would have been interesting to see the effect of including other covariates such as baseline MWD, or duration of IC.

A significant Improvement in patients' Quality of Life was reasonably developed and established during the clinical development of cilostazol via validated QoL instruments (SF-36 and WIQ). For other symptomatic treatments for PAD evaluated, a similar improvement in QoL has not been documented. Therefore, the utility values used in the economic model have been derived for all treatments from a regression model based on the MWD and SF-36 data assessed during cilostazol development. The improvement in patients' QoL through treatment with cilostazol cannot be similarly assumed for the whole class of PAD treatments discussed in the report. This is in particular the case as additional pharmacological effects of cilostazol have to be taken into consideration, all of which show positive effects on the arteriosclerotic processes of the disease and make its classification as a simple vasodilator inappropriate. Cilostazol is a selective PDE-III-Inhibitor and achieves its efficacy through increase in intracellular c-AMP concentration. As a result cilostazol exhibits its efficacy in three cell types, all involved in the genesis of atherosclerotic lesions: endothelia cells, smooth vascular muscle cells and thrombocytes. Additional effects are seen on lipid cells. Cilostazol

acts as an endothelial focussed antithrombotic, improves the endothelial cell functions, reduces the number of activated and partial activated thrombocytes and interrupts their interaction with activated endothelial cells. In addition, cilostazol acts as a vasodilator, has a positive effect on lipid metabolism and shows inhibition of cytokine production. Cilostazol therefore is certainly more than a pure thrombocyte aggregation inhibitor or a vasodilator. Cilostazol has also demonstrated clinical efficacy beyond intermittent claudication in exactly those risk areas having relevance for patients with arteriosclerotic diseases. Other products like naftidrofuryl have no such documented benefit. In a placebo-controlled, prospective trial (Gotoh, 2000, Cilostazol stroke prevention study) in over 1000 patients, cilostazol showed a high significant risk reduction of 41% and 38% for a re-stroke/stroke or myocardial infarction, respectively, compared to placebo.

A meta-analysis (Uchiyama 2009) across 12 randomised trials in 5674 patients for analysing the risk of cerebrovascular, cardiovascular or bleeding events showed a significant reduction in occurrence of stroke. Of those 5674 patients, 3782 patients were randomised in trials from cilostazol's development for Intermittent Claudication. In several East Asian countries cilostazol was recently approved for secondary stroke prevention. In a Cochrane Systematic Review (naftidrofuryl for acute stroke, Leonardi-Bee 2007) it was concluded that there is no evidence for the use of naftidrofuryl in acute stroke. In addition, in several placebo-controlled trials and meta-analyses cilostazol showed its effect at preventing re-stenosis including the number of necessary re-interventions following catheter interventions and stent applications in coronary arteries (Biondi-Zoccai 2008, Tamhane 2009). Also the open-rate after catheter intervention of the carotid and femoral was higher under treatment with cilostazol (Takigawa 2010).

Despite the fact that a submission for approval of the corresponding indications in Europe was not made, there is evidence that cilostazol improves the cardiovascular risk in patients with PAD. Presumably all these pharmacological and clinical effects described could contribute to cilostazol's improvement in patients' Quality of Life.

Drug cost

The Assessment Group used the generic cost of naftidrofuryl in the base case. However, in clinical practice, both the generic and the branded formulation are prescribed in England and Wales. Using Prescription Cost Analysis data for England, the proportion of prescriptions for naftidrofuryl as a generic versus branded formulation is 13% branded to 87% generic. As such the base case cost for naftidrofuryl might more accurately be re-weighted to reflect current clinical practice.

Model structure

Patients in "no vasoactive drug therapy" health state may not have placebo level MWD and utility, this is because patients may discontinue therapy after 24 weeks due to satisfactory response. Consequently the model may be more appropriately represented with health states that reflect health status rather than drug therapy status in the base case.

Health states in a Markov model should be mutually exclusive and each health state is assigned an estimate of costs and consequences. For example, in the "no vasoactive drug therapy" health state the Assessment Group assign no costs, and a walking distance (and thus

utility) associated with no vasoactive drug therapy (placebo) estimated from the meta-analysis. The Assessment Group did attempt to address this issue in sensitivity analysis (SA1) however due to the uncertainties in the base case due to missing data, results are unclear.

The main problem with this model specification is that patients in the "no vasoactive drug therapy" health state may not have placebo level walking distance and utility. This is because discontinuing patients after 24 weeks are often discontinuing therapy due to satisfactory response. The Assessment Group notes this on page 93 of the report: *"Expert clinical opinion suggests that many discontinuations beyond 24 weeks are likely to be due to the patient's condition improving or mortality"*. As such these individuals are likely to have a walking distance associated with vasoactive drug therapy.

The Assessment Group discounted the economic evaluation presented in a full published paper by Guest et al (2005) as a potential model structure for the following reasons:

1. There was not a no vasoactive drug comparator
2. The time horizon was 24 weeks
3. Effectiveness is only evaluated in terms of improvement in MWD. Health-related quality of life (utilities) was not evaluated
4. No model validation was reported

However, whilst the Assessment Group has extrapolated data beyond trial duration they have only been able to additionally model mortality, and discontinuations. Additionally, the discontinuation data beyond 24 weeks is based upon cilostazol data and large assumptions about how other drugs would compare to this cilostazol data. Therefore, it is unclear what additional information the Assessment Group is modelling by moving beyond 24 weeks.

Given that **1**, **3** and **4** could have been accounted for in the Assessment Group's representation of the Guest et al (2005) model, it is unclear why this economic evaluation was discounted, and perhaps should have been given more weight in the economic literature search.

<u>Model Inputs</u>

De Backer (2008) assessed Kieffer (2001), the single naftidrofuryl trial included in the meta-analysis and economic evaluation, as grading category B, "moderate risk of bias". In contrast, three cilostazol studies were classified as category A, and four as category B. As such, evidence for cilostazol was in general of greater quality than naftidrofuryl, as well as far greater quantity.

Discontinuation rates for patients within 24 weeks were based upon a meta-analysis of randomised controlled trials (RCTs) conducted by the Assessment Group. It is not clear in the write-up which studies were used to estimate the discontinuation rates. Assuming therefore that the discontinuation rate for naftidrofuryl was based only on Kieffer (2001), it is likely that the Assessment Group have incorrectly estimated the discontinuation rate for naftidrofuryl. Discontinuation rates were reported for Adhoute (1986); a paper included in the clinical literature search, and therefore could have been included in the analysis, as well as

for other 24 week naftidrofuryl trials that were excluded on the basis of the clinical literature search.

Long term discontinuation rates were taken from the only long term study by Hiatt (2008), a study for cilostazol. The Assessment Group claim that expert clinical opinion suggests that many discontinuations beyond 24 weeks may be due to patients improving rather than adverse events associated with the drug. In Hiatt (2008) 68% patients in the cilostazol arm discontinue the drug by 36 months. Due to lack of data the Assessment Group make the assumption that the long term discontinuation rate is the same as cilostazol for all other therapies. The figures generated for the 24 week discontinuation are subject to concern due to missing naftidrofuryl data and secondly, given that cilostazol is the only therapy to provide long term data there is complete uncertainty around the other therapies long-term discontinuation rates. As such, sensitivity should have been conducted that varied naftidrofuryl and pentoxifylline around a large range of values without varying cilostazol.

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