Assessment Group responses to comments from Otsuka Pharmaceuticals 02/03/11

Comment	Response
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.	The selection of trials included in the network meta-analysis followed a pre-planned protocol. A network meta-analysis does not impose any limitation on the number of trials in which each treatment needs to be evaluated or on the number of patients that are randomised to each treatment arm. Sampling variation and between study variability have been taken into account in the estimate of the population parameters. The use of different treadmill protocols may give rise to heterogeneity between studies and this has been quantified by allowing for heterogeneity in a random effects (network) meta-analysis. The assertion that the comparison does not represent a fair or scientifically valid comparison is unfounded.
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.	Our clinical experts suggested that this was appropriate given current evidence.
The Assessment Group may have over-estimated the clinical effectiveness of naftidrofuryl as a result of excluding studies. A number of naftidrofuryl studies were excluded by the Assessment Group	Maas (1984) was not included as it is the same study as Trubestein (1984), which was included in the narrative synthesis.

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. • 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) (This covers the clinical effectiveness and MWD sections, p3-6 of Otsuka comments on the ACD).	Adhoute (1990) and Moody (1994) were excluded because they did not evaluate the licensed doses of the drugs. Naftidrofuryl fumalate is not included within the MHRA website or the BNF. Non-English language articles are frequently excluded unless the abstract shows that the study would be highly valuable. Although there is potential for bias, it does not tend to cause bias, as we have referenced in section 8.2 of the report. Boccalon (2001) should be excluded on the basis of language only within the report. Adhoute (1986) was excluded from the meta-analysis and hence the economic evaluation as it did not provide suitable data on MWD or PFWD. However, the Cochrane Review on Naftidrofuryl for Intermittent Claudication by de Backer TLM, Vander Stichele R, Lehert P, Van Bortel L (http://www2.cochrane.org/reviews/en/ab001368.html) does appear to have data on MWD and PFWD from this study, although it is not possible to validate it from the Adhoute (1986) publication. Nevertheless, the assessment group have undertaken an additional sensitivity analysis including this data to assess their impact on the conclusions. These results are shown in the Appendix of this document.
They may also have underestimated the drug cost used in clinical practice.	The small proportion of clinicians that may be prescribing branded naftidrofuryl is small and would have minimal impact upon the model results.
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.	This parameter was tested within the sensitivity analysis and had very little impact upon the model results. Given that the model results are not sensitive to these parameters, varying them more widely would have minimal impact upon the model results.
The model structure used may underestimate the benefit of cilostazol in	This was tested within the sensitivity analysis and suggested a limited

terms of discontinuing patients being assigned a placebo utility.	impact upon the model results.
The model may more appropriately have been developed with health states related to functional ability, and not health states related to treatments.	There was insufficient evidence to model states in this way.
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.	The issue about whether two drugs are required is for the committee. As stated in the ACD, even in the absence of naftidrofuryl, cilostazol has a cost per QALY gained in excess of £30,000.
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.	Uncertainty in the model to estimate utility was incorporated into the PSA. Several regressions were tested during the model development process; however the model specification used was the most reasonable given the available data.
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	In addition to the four reasons for discounting the Guest et al (2005) model, Guest et al (2005) used effectiveness estimates which were calculated separately for each drug as a weighted mean based on the sample size of the identified trials. Two trials were included of cilostazol[60,55] and three trials were included of naftidrofuryl oxalate.[92,93,64] The two included trials of cilostazol were the two trials demonstrating the greatest effectiveness of cilostazol at that time, whilst two of the three trials of naftidrofuryl oxalate included within the analysis assess a dose which is not currently licensed within England and Wales. In comparison, the assessment group model used a random effects mixed treatment comparison to estimate effectiveness.

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.	
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.	The quality of the included studies was assessed within the assessment report (see assessment report for further details) and the paper by Kieffer (2001) was classified as being of relatively good quality. The number of trials in each category is not sufficient in itself to say that the results of the meta-analysis is more or less robust as this will depend on the magnitude of any bias and the amount of information coming from each trial.

Appendix: Additional sensitivity analysis including data from Adhoute (1986) within the meta-analysis and economic model

This sensitivity analysis includes an additional study of naftidrofuryl oxalate within the meta-analysis based upon a review of naftidrofuryl studies by De Backer (2008). Within the review the MWD outcomes are included within a table and are not described within the text, meaning that we do not have confirmation of our interpretation of the numbers within the table. It is unclear exactly where these numbers have come from as they were not reported within the paper by Adhoute *et al.* (1986). However, it was thought that given Otsuka's concerns it would be useful as a sensitivity analysis to understand the potential implications of including this study within the meta-analysis and economic model since it met the study inclusion criteria.

Results of meta-analysis: MWD

Table 1 compares the original results of the meta-analysis for MWD with the results including the additional study data

Table 1: Posterior distribution for the change from baseline in log-mean MWD (log metres)

	Original Results Mean 95% Credible Interval	**Results of Sensitivity Analysis Mean 95% Credible Interval**
Cilostazol random effects	0.220 (0.108, 0.337)	0.219 (0.102, 0.335)
Cilostazol predictive distribution	0.220 (-0.072, 0.511)	0.218 (-0.064, 0.512)
Pentoxifylline random effects	0.101 (-0.016, 0.217)	0.100 (-0.015, 0.218)
Pentoxifylline predictive distribution	0.101 (-0.195, 0.383)	0.101 (-0.188, 0.393)
Naftidrofuryl random effects	0.472 (0.181, 0.762)	0.343 (0.133, 0.552)
Naftidrofuryl predictive distribution	0.472 (0.087, 0.865)	0.340 (0.007, 0.674)
Between-study SD	0.125 (0.068, 0.220)	0.126 (0.069, 0.218)

Note: The differences between the original and revised results for cilostazol and pentoxifylline are due to random sampling error.

Table 1 suggests that the inclusion of an additional study by Adhoute *et al*. (1986) reduces the estimated effectiveness of naftidrofuryl oxalate in terms of MWD.

However, naftidrofuryl continues to have a significant effect and the order of the effect remains the same.

Results of meta-analysis: PFWD

Table 2 compares the original results of the meta-analysis for PFWD with the results including the additional study data

Table 2: Posterior distribution for the change from baseline in log-mean PFWD (log metres)

	Original Results Mean 95% Credible Interval	**Results of Sensitivity Analysis Mean 95% Credible Interval**
Cilostazol random effects	0.126 (0.024, 0.226)	0.126 (0.024, 0.233)
Cilostazol predictive distribution	0.126 (-0.107, 0.359)	0.127 (-0.106, 0.367)
Pentoxifylline random effects	0.088 (-0.017, 0.195)	0.086 (-0.019, 0.194)
Pentoxifylline predictive distribution	0.087 (-0.153, 0.326)	0.086 (-0.151, 0.326)
Naftidrofuryl random effects	0.495 (0.231, 0.764)	0.405 (0.205, 0.604)
Naftidrofuryl predictive distribution	0.496 (0.157, 0.845)	0.405 (0.107, 0.690)
Between-study SD	0.095 (0.032, 0.184)	0.096 (0.030, 0.188)

Table 2 suggests that the inclusion of an additional study by Adhoute *et al*. (1986) reduces the estimated effectiveness of naftidrofuryl oxalate in terms of PFWD. However, as for MWD, naftidrofuryl continues to have a significant effect and the order of the effect remains the same.

Results of health economic model

The results of the health economic model when inputting the results of the meta-analysis above are shown in Tables 3 and 4 below.

Table 3: Original discounted deterministic results

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	Incremental cost-effectiveness ratio (£ per QALY gained)	Dominance
No vasoactive drug (baseline technology)	£0	4.981	-	
Pentoxifylline	£493	4.989		Dominated by naftidrofuryl oxalate
Cilostazol	£964	5.000		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	£298	5.024	£6,070	

Table 4: Discounted deterministic results with above meta-analysis including additional study data

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	Incremental cost-effectiveness ratio (£ per QALY gained)	Dominance
No vasoactive drug (baseline technology)	£0	4.981	-	
Pentoxifylline	£493	4.989		Dominated by naftidrofuryl oxalate
Cilostazol	£964	5.000		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	£298	5.017	£8,321	

These results suggest that the inclusion of the additional naftidrofuryl oxalate data within the meta-analysis has a limited impact upon the economic model results. Cilostazol and pentoxifylline continue to be dominated by naftidrofuryl oxalate and the cost per QALY gained for naftidrofuryl oxalate increases from £6,070 to £8,321.

References

- Adhoute G, Bacourt F, Barral M, Cardon JM, Chevalier JM, Cuny A, et al. Naftidrofuryl in chronic arterial disease. Results of a six month controlled multicenter study using Naftidrofuryl tablets 200 mg. Angiology1986 Mar; 37(3 Pt 1):160-7.
- De Backer TL, Vander Stichele R, Lehert P, Van Bortel L. Naftidrofuryl for intermittent claudication. Cochrane Database Syst Rev2008 (2):CD001368.