NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document and evaluation report for the above health technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation.	Comment noted.
NHS Salford	On behalf of NHS Salford, I would like to submit our comments on the appraisal consultation document for the Multiple Technology Appraisal on cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease in the NHS in England and Wales. NHS Salford is in agreement with the appraisal committee's decision that this technology does represent a cost effective use of scarce NHS resources. •**Naftidrofuryl gave the greatest increase in maximum walking distance relative to placebo.** Twenty-six relevant trials were identified. Amongst trials assessing maximum walking distance, one of two trials of naftidrofuryl, seven of ten trials of cilostazol, two of eight trials of pentoxifylline demonstrated greater improvement in maximum walking distance vs. placebo. One placebo-controlled trial of inositol found no significant benefit. Network meta-analysis conducted by the Assessment Group showed that naftidrofuryl gave the greatest increase from baseline in log mean maximum walking distance (relative increase in log mean maximum walking distance; 60.3% vs. 24.6% with cilostazol and 10.6% with pentoxifylline). The 95% credible intervals demonstrated a significant effect for naftidrofuryl and cilostazol, though the wide intervals implied uncertainty about the size of the true effect.	Comment noted. Comment noted.

Consultee	Comment	Response
NHS Salford	•**Naftidrofuryl improves other outcomes not considered by specialists to have direct clinical significance to the management of peripheral arterial disease.** Pain-free walking distance was increased relative to placebo in four of five trials of naftidrofuryl, five of ten trials of cilostazol, and two of seven trials of pentoxifylline. Using network meta-analysis, the maximum benefit was seen for naftidrofuryl (relative increase in pain-free walking distance; 64.2% with naftidrofuryl compared to 13.4% with cilostazol and 9.2% with pentoxifylline). Clinical specialists consider neither pain-free walking distance nor the ankle brachial pressure index to be clinically relevant outcome measures, and the Appraisal Committee agreed that the most appropriate focus should be upon maximum walking distance. •**There are no major concerns regarding the safety of naftidrofuryl and the vasoactive drugs studied.** The included studies identified no increased rate of serious adverse events with any of the drugs and no mortality or cardiovascular risk relative to placebo. Though the trials were not designed to assess long-term safety, there is post marketing data available and based on all currently available information, there are no major concerns regarding the safety of these drugs. •**Annual per patient costs for naftidrofuryl would be up to £117.48 for the generic preparation and £214.68 for the branded preparation.** NICE made these estimations based on acquisition drug costs alone using British National Formulary 60 costs (excluding VAT). The best estimate for an average PCT of 300,000 people is a prevalence of 5,766 (62% of 300,000 population x 3.1% prevalence) patients with symptomatic peripheral arterial disease who may be eligible. A preliminary assessment suggests that if the lowest dose generic preparation was used the maximum cost would therefore be in the region of £339,041 per year for a population of 300,000.The	Comment noted. Comment noted Comment noted. The potential budget impact of the adoption of a technology does not determine the Appraisal Committee's decision. See Guide to the Methods of Technology Appraisal section 6.2.14 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

Consultee	Comment	Response
NHS Salford	potential budget impact for a PCT would depend on the numbers of patients currently receiving vasoactive drugs for peripheral arterial disease, and the preparations currently prescribed. Vasoactive drugs provide symptomatic benefit only and have no effect upon disease progression or survival. •**There were limitations to the quality of the research; including a lack of direct comparisons.** Three head-to-head trials of cilostazol and pentoxifylline were identified, only one of which demonstrated superiority of cilostazol and was published. All trials were of typically short duration, mostly 24 weeks, though benefit was usually noted by 12 weeks and trial duration was not considered to lead to uncertainty of effect. Some trials had considered the wider pharmacological and lifestyle aspects of care, but few reported the patient's prior response to supportive care and exercise management. Evidence for inositol nicotinate is poor; amongst three RCTs only one examined maximum walking distance and none evaluated pain-free walking distance; this precluded inclusion of this drug in the network meta-analysis. Only one trial of naftidrofuryl could be included in the meta-analysis.	Comment noted.
Otsuka	**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,	Comment noted. The Committee cannot speculate about the deliberations of other bodies. NICE and other institutions make decisions using different processes.

Consultee	Comment	Response
Otsuka	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.	Comment noted. The Committee noted the concerns raised by the manufacturer of cilostazol about the inclusion of trials that used different treadmill protocols, but acknowledged that any differences that might exists between trials had been quantified by the use of a random effects network meta-analysis. The Committee accepted that the heterogeneity in the trials could lead to bias in the estimated effectiveness of these drugs, but was persuaded that the relative benefits in terms of improvement in maximum walking distance was plausible given the empirical data. See FAD section 4.3.10 Comment noted. The Committee noted that the manufacturer had not submitted any evidence related to these potential benefits in its original submission or during consultation. The Committee was aware that the marketing authorisation for cilostazol in the UK did not go beyond the treatment of intermittent claudication. The Committee concluded that there were no benefits other than improvement in maximum walking distance related to health-related quality of life. See FAD section 4.3.16
Otsuka	**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	Comment noted. Trials were excluded if: duration was less than 24 weeks; data on

Consultee	Comment	Response
Ostuka	may also have underestimated the drug cost used in clinical practice.	maximum walking distance were not reported or were reported in a way that did not allow comparison of results across trials; the trial did not evaluate the licensed doses of the drug; or the trial was published in a language other than English. The Committee accepted the Assessment Group's rationale for including only one trial of naftidrofuryl oxalate in the meta-analysis and agreed that the Assessment Group's process was transparent. See FAD section 4.3.11 In response to comments received from consultation the Assessment Group undertook a sensitivity analysis that included data from a trial of naftidrofuryl oxalate that it had excluded from its network meta-analysis. The inclusion of this trial in the meta-analysis resulted in a reduction in the estimated effectiveness of naftidrofuryl oxalate but that naftidrofuryl oxalate continued to have a significant effect and its effectiveness relative to the other vasoactive drugs did not change. The Committee concluded that the Assessment Group may have originally over-estimated the clinical effectiveness of naftidrofuryl oxalate as a result of excluding trials but was persuaded by the evidence presented that naftidrofuryl oxalate continued to have the largest effect compared with cilostazola and pentoxifylline. See FAD sections 4.2.13 and 4.3.12. The Assessment Group explored the impact on

Consultee	Comment	Response
Ostuka		the ICER of using the price of branded preparation of naftidrofuryl oxalate in a sensitivity analysis, which increased the ICER to £11,060 per QALY gained. The Committee concluded that treatment with naftidrofuryl oxalate should be started with the least costly licensed preparation. See FAD sections 4.2.11, 4.3.17 and 1.1
	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.	Comment noted. The Assessment Group undertook sensitivity analysis in which alternative rates of long term discontinuation were used. The results of the sensitivity analyses indicated that the ICERs of naftidrofuryl oxalate were relatively insensitive to alternative long-term discontinuation rates. See FAD section 4.2.11.
	3. The model structure used may underestimate the benefit of cilostazol in terms of discontinuing patients being assigned a placebo utility.	The Assessment Group undertook one-way sensitivity analyses using alternative baseline utility values. The results indicated that the ICERs of naftidrofuryl oxalate were relatively insensitive to baseline utility values. See FAD section 4.2.11
	4. The model may more appropriately have been developed with health states related to functional ability, and not health states related to treatments.	Comment noted. The Committee examined the economic modelling developed for the appraisal and agreed that the Assessment Group's economic model was of good quality. See FAD section 4.3.15.
Otsuka	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**	

Consultee	Comment	Response
	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?"	Comment noted. The Committee considered the ICERs derived from the Assessment Group's economic model of £50,700, £6070, £11,060 and £54,800 per QALY gained for cilostazol, generic naftidrofuryl oxalate, branded naftidrofuryl oxalate and pentoxifylline, respectively, when each was compared with placebo. The Committee agreed that it could not consider cilostazol and pentoxifylline appropriate treatment options, because naftidrofuryl oxalate dominates cilostazol and pentoxifylline. The Committee noted, the ICERs for cilostazol and pentoxifylline compared with placebo exceeded those normally considered to be an acceptable use of NHS resources. The Committee concluded that cilostazol and pentoxifylline could not be recommended as a cost-effective use of NHS resources for those people with contraindications to naftidrofuryl oxalate. See FAD section 4.3.17. The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources ('Guide to the Methods of Technology Appraisal', paragraphs 6.2.6.1–6.2.6.3; see URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

Consultee	Comment	Response
Otsuka	Otstuka comments on the evaluation report	Comment noted. These comments relate to the assessment report rather than the ACD. No action required for the FAD.
Royal College of Nursing	**Has the relevant evidence has been taken into account?** The evidence considered seems comprehensive.	Comment noted.
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with peripheral arterial disease. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted.
Royal College of Nursing	**Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?** Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted.
Royal College of Nursing	**Are there any equality related issues that need special consideration that are not covered in the ACD?** We are not aware of any specific issue at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate. Any guidance on the use of this technology should also be mindful of the impact it may have on reducing socio-economic inequalities.	Comment noted. No equality issues had been raised during the scoping, evidence submissions or consultation stages. Therefore, it concluded that there were no specific issues relating to equality that needed to be taken into account. See FAD section 4.3.19.

Consultee	Comment	Response
Vascular Society of Great Britain and Ireland	**Has all of the relevant evidence been taken into account?** We believe that the evaluation has been thorough and that the evidence considered is appropriate, although there are some omissions (see below). We are however disappointed not to see the name of a Vascular Surgeon on the panel and I understand that this will is being addressed for future reviews. We are also concerned that the only clinician involved with actual experience of treating claudication in clinical practice was nominated by Otsuka. This "conflict of interest" requires a declaration in the published guidance. It is of interest that the conclusions are based a single meta-analysis which included only a single trial of naftidrofuryl. There are many contradictory RCTs published, and it would have been healthier had the committee looked at a fuller spectrum of outcomes. How was publication bias excluded ie if there is a significant inverse relationship between sample size and response, it suggests bias produced by non-publication of negative results. The publications span from 1989 to 2009 and exclude a couple of important earlier British RCTs of naftidrofuryl from respected units which concluded that it was not effective in claudication (Ruckley et al BMJ 1978; 1: 622 and Clyne et al, Br J Surg 1980; 67: 347).	Comment noted. Only one nomination was received from the manufacturer of cilostazol (Otsuka). Professional groups were sent reminders for nominations but none were received. However, the representative from the Clinical Development Group is a Professor of Vascular Surgery and attended the Appraisal Committee meeting. Comment noted. Trials were excluded if: duration was less than 24 weeks; data on maximum walking distance were not reported or were reported in a way that did not allow comparison of results across trials; the trial did not evaluate the licensed doses of the drug; or the trial was published in a language other than English. The Committee accepted the Assessment Group's rationale for including only one trial of naftidrofuryl oxalate in the meta-analysis and agreed that the Assessment Group's process was transparent. See FAD section 4.3.11. In response to comments received from consultation the Assessment Group undertook a sensitivity analysis that included data from a trial of naftidrofuryl oxalate that it had excluded from its network meta-analysis. The inclusion of this trial in the meta-analysis resulted in a reduction in the estimated effectiveness of naftidrofuryl oxalate but that naftidrofuryl
Vascular Society of Great		

Consultee	Comment	Response
Britain and Ireland		oxalate continued to have a significant effect and its effectiveness relative to the other vasoactive drugs did not change. The Committee concluded that the Assessment Group may have originally over-estimated the clinical effectiveness of naftidrofuryl oxalate as a result of excluding trials but was persuaded by the evidence presented that naftidrofuryl oxalate continued to have the largest effect compared with cilostazola and pentoxifylline. See FAD sections 4.2.13 and 4.3.12.
Vascular Society of Great Britain and Ireland	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The recommendation of the use of vasoactive drugs is not sound as it has not been placed into context with other treatments (stopping smoking, aspirin etc). We would be concerned that, as it stands, vasoactive drugs will be used by GP Commissioners as the first line treatment and may delay referral for other more appropriate treatments.	Comment noted. The Committee was aware that a NICE clinical guideline on 'Lower limb peripheral arterial disease: diagnosis and management' is being developed to help define clinical practice, and that this appraisal would contribute to this guideline. For the purpose of this guidance, and reflecting the scope for this appraisal, the Committee concluded that it would only be appropriate to consider the use of vasodilators after taking into account other treatment options, for example exercise and also treatment to reduce the risk of cardiovascular events. The Committee was aware that the clinical and cost effectiveness of the vasoactive drugs may vary depending on their place in the treatment pathway. However, the Committee concluded that its remit was to appraise cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate in a situation where vasodilator
Vascular Society of Great		

Consultee	Comment	Response
Britain and Ireland		therapy is deemed the most appropriate treatment option amongst the other treatment options available, such as exercise therapy or angioplasty, that is where the vasodilator drugs would be compared with each other and with best supportive case. The Committee also concluded that the use of drug treatment should not replace referral for consideration of specialist treatment. See FAD sections 1.1 and 4.3.3.
Vascular Society of Great Britain and Ireland	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The assessment of benefit is based on a range of quality of life markers and maximum walking distance. We felt that the clinical utility of these is not clearly established and the assessment does not make this clear e.g. It is one thing to get patients to walk 50m further on a treadmill, but does that make any difference to their day to day existence.	Comment noted. The Committee acknowledged that assessing maximum pain-free walking distance can be difficult to interpret without using the fixed-speed treadmill because patients usually adjust the speed of their walking to avoid pain and to maximise walking distance. The Committee agreed that it was appropriate to focus on the Assessment Group's analyses of maximum walking distance. The Committee heard from the clinical specialist that a clinically significant improvement in maximum walking distance approximated 50 meters, or, in relative terms, a 100% increase. The Committee recognized that the evidence showed that cilostazol and naftidrofuryl oxalate clinically significantly improved maximum walking distance compared with placebo. See FAD sections 4.3.6 and 4.3.7.
Vascular Society of Great	More specifically, your recommendations are primarily based on the Health Economics, which are derived from a Markov model, which in turn is based	Comment noted. The Committee acknowledged this uncertainty but noted that

Consultee	Comment	Response
Britain and Ireland	on SF36 QoL data from one trial comparing cilostazol with no vasoactive treatment in 106 patients. There has then been extrapolation of walking distance into quality of life benefits, to calculate QALYs gained and ICERs. There is little / no QoL data to directly support naftidrofuryl.	the order of the utility values was consistent with the order of effectiveness of the vasoactive drugs as shown in the meta-analysis. The Committee was aware that commentators had called for future research to better quantify the association between clinical endpoints relevant to peripheral arterial disease and quality of life. The Committee also recognised the limited published evidence for quality of life associated with these drugs, and agreed that the approach used by the Assessment Group to obtain utility values for the economic model was acceptable, while proposing that further research be undertaken. See FAD section 4.3.15.
Vascular Society of Great	There was no real consideration to the range of patients nor the degree of disability suffered by patients. Some of the studies looked at very long distance claudicants. Do these recommendations therefore still pertain to a 20m claudicant?	Comment noted. The Committee was aware that the size of the treatment effect reported in the trials for each of the drugs varied. The Committee heard from the Assessment Group that this variation resulted from changes in standard clinical practice over time, which are reflected in the fact that the publication dates of the included trials span 20 years (from 1989 to 2009). The Committee heard from the clinical specialist that a clinically significant improvement in maximum walking distance approximated 50 meters, or, in relative terms, a 100% increase. However, the Committee recognised that the evidence for cilostazol and naftidrofuryl oxalate showed that there was a clinically significant improvement in maximum walking distance compared with the placebo groups. See FAD section 4.3.7.

Consultee	Comment	Response
Britain and Ireland	We felt that the role of other treatments for claudication needs to be more clearly described. At present it gives the impression that angioplasty is the first line treatment.	Comment noted. The Committee was aware that a NICE clinical guideline on 'Lower limb peripheral arterial disease: diagnosis and management' is being developed to help define clinical practice, and that the current appraisal would contribute to this guideline. For the purpose of this guidance, and reflecting the scope for this appraisal, the Committee concluded that it would only be appropriate to consider the use of vasodilators after taking into account other treatment options, for example exercise and also treatment to reduce the risk of cardiovascular events. The Committee was aware that the clinical and cost effectiveness of the vasoactive drugs may vary depending on their place in the treatment pathway. However, the Committee concluded that its remit was to appraise cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate in a situation where vasodilator therapy is deemed the most appropriate treatment option amongst the other treatment options available, such as exercise therapy or angioplasty, that is where the vasodilator drugs would be compared with each other and with best supportive case. The Committee also concluded that the use of drug treatment should not replace referral for consideration of specialist treatment. See FAD sections 1.1 and 4.3.3.
Vascular Society of Great		Comment noted. The Committee discussed the

Consultee	Comment	Response
Britain and Ireland	We have some concern regarding the high side effect profile of Cilostazol and are not convinced with your conclusion that there is no difference amongst all agents examined. We are not convinced that the data available is able to support this statement.	adverse events seen in the trials of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate. It noted that the data from the trials suggested that non-serious adverse events (such as headaches and gastrointestinal complaints) and serious adverse events (such as cardiovascular events and death) did not differ between the groups given vasoactive drugs and those given placebo. The Committee also noted that the clinical specialist did not have concerns about the long-term safety of the vasoactive drugs. The Committee concluded that based on the currently available information, there were no major concerns about the adverse effects of vasodilator drugs. See FAD section 4.3.14.
	We are further concerned that the moderate patient benefit described could result in widespread prescription of naftidrofuryl oxalate, before an appropriate cost benefit analysis has been performed. We find difficulty with seeing how this would translate into meaningful patient benefit.	The Committee considered the clinical and cost-effectiveness of naftidrofuryl oxalte, cilostazol, pentoxifylline and inositol nicotinate. The Committee concluded that based on the Assessment Group's network meta-analysis, cilostazol, naftidrofuryl oxalate and pentoxifylline improved maximum walking distance compared with placebo. See FAD section 4.3.13
Vascular Society of Great		The Committee examined the economic model developed for the appraisal and agreed that the Assessment Group's model was of good quality. The Committee concluded that naftidrofuryl oxalate could be recommended as a cost-effective use of NHS resources while cilostazol, pentoxifylline and inositol nicotinate

Consultee	Comment	Response
Britain and Ireland		could not be recommended. See FAD sections 4.3.15, 4.3.17 and 4.3.18.
Vascular Society of Great Britain and Ireland	**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?** We have no concerns with this section.	Comment noted.
Vascular Society of Great Britain and Ireland	**Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?"** We have no concerns with this aspect.	Comment noted.
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment on this appraisal. Please note that we have no comment to submit at this stage.	Comment noted.

Commentator	Comment	Response
Commissioning Support Appraisals	On behalf of NHS Salford, I would like to submit our comments on the appraisal consultation document for the Multiple Technology Appraisal on cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease in the NHS in England and Wales. NHS Salford is in agreement with the appraisal committee's decision that this technology does represent a cost effective use of scarce NHS resources.	Comment noted.
Commissioning Support Appraisals	•**Naftidrofuryl gave the greatest increase in maximum walking distance relative to placebo.** Twenty-six relevant trials were identified. Amongst trials assessing maximum walking distance, one of two trials of naftidrofuryl, seven of ten trials of cilostazol, two of eight trials of pentoxifylline demonstrated greater improvement in maximum walking distance v.s. placebo. One placebo-controlled trial of inositol found no significant benefit. Network meta-analysis conducted by the Assessment Group showed that	

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	naftidrofuryl gave the greatest increase from baseline in log mean maximum walking distance (relative increase in log mean maximum walking distance; 60.3% vs. 24.6% with cilostazol and 10.6% with pentoxifylline). The 95% credible intervals demonstrated a significant effect for naftidrofuryl and cilostazol, though the wide intervals implied uncertainty about the size of the true effect.	Comment noted.
	•**Naftidrofuryl improves other outcomes not considered by specialists to have direct clinical significance to the management of peripheral arterial disease.** Pain-free walking distance was increased relative to placebo in four of five trials of naftidrofuryl, five of ten trials of cilostazol, and two of seven trials of pentoxifylline. Using network meta-analysis, the maximum benefit was seen for naftidrofuryl (relative increase in pain-free walking distance; 64.2% with naftidrofuryl compared to 13.4% with cilostazol and 9.2% with pentoxifylline). Clinical specialists consider neither pain-free walking distance nor the ankle brachial pressure index to be clinically relevant outcome measures, and the Appraisal Committee agreed that the most appropriate focus should be upon maximum walking distance.	Commented noted
	•**There are no major concerns regarding the safety of naftidrofuryl and the vasoactive drugs studied.** The included studies identified no increased rate of serious adverse events with any of the drugs and no mortality or cardiovascular risk relative to placebo. Though the trials were not designed to assess long-term safety, there is post marketing data available and based on all currently available information, there are no major concerns regarding the safety of these drugs.	Comment noted. The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources ('Guide to the Methods of Technology Appraisal', paragraphs 6.2.6.1–
	•**Annual per patient costs for naftidrofuryl would be up to £117.48 for the generic preparation and £214.68 for the branded preparation.** NICE made these estimations based on acquisition drug costs alone using British National Formulary 60 costs (excluding VAT). The best estimate for an average PCT of 300,000 people is a prevalence of 5,766 (62% of 300,000 population x 3.1% prevalence) patients with symptomatic peripheral arterial	

Commentator	Comment	Response
	disease who may be eligible. A preliminary assessment suggests that if the lowest dose generic preparation was used the maximum cost would therefore be in the region of £339,041 per year for a population of 300,000. The potential budget impact for a PCT would depend on the numbers of patients currently receiving vasoactive drugs for peripheral arterial disease, and the preparations currently prescribed. Vasoactive drugs provide symptomatic benefit only and have no effect upon disease progression or survival. •**There were limitations to the quality of the research;** including a lack of direct comparisons. Three head-to-head trials of cilostazol and pentoxifylline were identified, only one of which demonstrated superiority of cilostazol and was published. All trials were of typically short duration, mostly 24 weeks, though benefit was usually noted by 12 weeks and trial duration was not considered to lead to uncertainty of effect. Some trials had considered the wider pharmacological and lifestyle aspects of care, but few reported the patient's prior response to supportive care and exercise management. Evidence for inositol nicotinate is poor; amongst three RCTs only one examined maximum walking distance and none evaluated pain-free walking distance; this precluded inclusion of this drug in the network meta-analysis. Only one trial of naftidrofuryl could be included in the meta-analysis.	6.2.6.3; see URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf Comment noted.
National Clinical Guideline Centre	**Has all of the relevant evidence been taken into account?** We are satisfied that all the relevant evidence has been taken into account.	Comment noted.
National Clinical Guideline Centre	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The GDG would like to comment on the use of maximum walking distance (MWD) as the main outcome indicator and the use of MWD as an accurate measure to calculate quality of life (QoL) in patients with intermittent claudication.	Comment noted. Assessing pain-free walking distance can be difficult to interpret without using the fixed-speed treadmill because patients usually adjust the speed of their

Commentator	Comment	Response
		walking to avoid pain and to maximise walking distance. The Committee agreed that it was appropriate to focus on the Assessment Group's analyses of maximum walking distance. See FAD section 4.3.6.
	We acknowledge the lack of outcome data directly measuring QoL in the randomised trials and the choice of MWD as the main indicator of outcomes because of the limited availability of better outcome data. However we are concerned that the ACD does not reflect the limitations in using MWD or the uncertainty in the use of MWD to calculate QoL. We are keen to see these limitations reflected in the TA and a research recommendation that future studies should include outcome measures that more accurately reflect patient quality of life and functional ability.	Comment noted. The Committee acknowledged this uncertainty but noted that the order of the utility values was consistent with the order of effectiveness of the vasoactive drugs as shown in the meta-analysis. The Committee was aware that commentators had called for future research to better quantify the association between clinical endpoints relevant to peripheral arterial disease and quality of life. The Committee also recognised the limited published evidence for quality of life associated with these drugs, and agreed that the approach used by the Assessment Group to obtain utility values for the economic model was acceptable, while proposing that further research be undertaken. See FAD section 4.3.15.
National Clinical Guideline Centre	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **Section 4.3.3:** We are concerned this section may imply that angioplasty is first line treatment for this group of patients. This is not the case, though there are patients where the use of vasoactive drugs to try and delay angioplasty does not appear to have a valid rationale and angioplasty maybe an appropriate initial therapy. We would be keen to see this clarified in the document.	Comment noted. The Committee was aware that a NICE clinical guideline on 'Lower limb peripheral arterial disease: diagnosis and management' is being developed to help define clinical practice, and that this appraisal would contribute to this guideline. For the purpose of this guidance, and reflecting the scope for this appraisal, the Committee concluded that it would only be appropriate to consider the use
National		

Commentator	Comment	Response
Clinical Guideline Centre		of vasodilators after taking into account other treatment options, for example exercise and also treatment to reduce the risk of cardiovascular events. The Committee was aware that the clinical and cost effectiveness of the vasoactive drugs may vary depending on their place in the treatment pathway. However, the Committee concluded that its remit was to appraise cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate in a situation where vasodilator therapy is deemed the most appropriate treatment option amongst the other treatment options available, such as exercise therapy or angioplasty, that is where the vasodilator drugs would be compared with each other and with best supportive case. The Committee also concluded that the use of drug treatment should not replace referral for consideration of specialist treatment. See FAD sections 1.1 and 4.3.3.
National Clinical Guideline Centre	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** There is concern over the lack of clarity where naftidrofuryl oxalate should be used in comparison with other treatments available for claudication. The GDG are concerned that the recommendation could be interpreted as proposing naftidrofuryl oxalate as first line therapy for claudication in preference to exercise or endovascular treatment. We acknowledge this issue will be clarified in the clinical guideline and this is noted in section 4.3.2 but suggest this could be emphasised earlier perhaps as an extra sentence in section 1.1or in section 2.8.	Comment noted. Please see previous response
National Clinical	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any**	

Commentator	Comment	Response
Guideline Centre	**group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** None were noted by the group.	Comment noted.
NHS Quality Improvement Scotland	**Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?** I consider that all relevant evidence has been included.	Comment noted.
NHS Quality Improvement Scotland	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations?** The summaries states that the "committtee accepted the rationale for only including one trial of naftidrofuryl oxalate in the meta-analysis". This was my main objection to the meta-analysis. My other objection regarding the lack of quality of life evidence and the derivation of utility values has been addressed in 4.3.14.	Comment noted. Trials were excluded if: duration was less than 24 weeks; data on maximum walking distance were not reported or were reported in a way that did not allow comparison of results across trials; the trial did not evaluate the licensed doses of the drug; or the trial was published in a language other than English. The Committee accepted the Assessment Group's rationale for including only one trial of naftidrofuryl oxalate in the meta-analysis and agreed that the Assessment Group's process was transparent. See FAD section 4.3.11. In response to comments received from consultation the Assessment Group undertook a sensitivity analysis that included data from a trial of naftidrofuryl oxalate that it had excluded

Commentator	Comment	Response
NHS Quality Improvement Scotland		from its network meta-analysis. The inclusion of this trial in the meta-analysis resulted in a reduction in the estimated effectiveness of naftidrofuryl oxalate but that naftidrofuryl oxalate continued to have a significant effect and the effectiveness relative to the other vasoactive drugs did not change. The Committee concluded that the Assessment Group may have originally over-estimated the clinical effectiveness of naftidrofuryl oxalate as a result of excluding trials but was persuaded by the evidence presented that naftidrofuryl oxalate continued to have the largest effect compared with cilostazola and pentoxifylline. See FAD sections 4.2.13 and 4.3.12.
NHS Quality Improvement Scotland	**Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound?** The recommendations are reasonable	Comment noted.
NHS Quality Improvement Scotland	**Are the patient pathways and treatment options described in the assessment applicable to NHS Scotland? If not, how do they differ in Scotland?** Yes.	Comment noted.
NHS Quality Improvement Scotland	**Would the provisional recommendations change the patient pathways and/or patient numbers in NHS Scotland? If so, please describe what these changes would be.** No they are consistent with the SIGN guidelines on management of patients with PAD.	Comment noted.
NHS Quality	**Do you think there is any reason why this provisional guidance would**	

Commentator	Comment	Response
Improvement Scotland	**not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.** No.	Comment noted.

Comments received from members of the public

Role*	Section	Comment	Response
NHS professional 1	1	There is nothing here with which I would disagree.	Comment noted.
NHS Professional 1	2	There is nothing here with which I would disagree.	Comment noted.
NHS Professional 1	3	There is nothing here with which I would disagree.	Comment noted.
NHS Professional 1	4	There is nothing here with which I would disagree.	Comment noted.
NHS professional 1	5	There is nothing here with which I would disagree.	Comment noted.
NHS professional 1	6	There is nothing here with which I would disagree.	Comment noted.
NHS professional 1	7	No comment.	Comment noted.
NHS professional 1	8	There is nothing here with which I would disagree.	Comment noted.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS professional 2	1	I agree with the guidance issued by NICE as they have recommended the agent with the best evidence base. The other agents not recommended not only have a weaker evidence base but are more costly to the NHS and should not be used in the NHS.	Comment noted.
NHS professional 3	3	Annual per patient costs for naftidrofuryl would be up to £117.48 for the generic preparation and £214.68 for the branded preparation. NICE made these estimations based on acquisition drug costs alone using British National Formulary 60 costs (excluding VAT). The best estimate for an average PCT of 300,000 people is a prevalence of 5,766 (62% of 300,000 population x 3.1% prevalence) patients with symptomatic peripheral arterial disease who may be eligible. A preliminary assessment suggests that if the lowest dose generic preparation was used the maximum cost would therefore be in the region of £339,041 per year for a population of 300,000. The potential budget impact for a PCT would depend on the numbers of patients currently receiving vasoactive drugs for peripheral arterial disease, and the preparations currently prescribed. Vasoactive drugs provide symptomatic benefit only and have no effect upon disease progression or survival.	Comment noted. The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources ('Guide to the Methods of Technology Appraisal', paragraphs 6.2.6.1–6.2.6.3; see URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

Role*	Section	Comment	Response
NHS professional 3	4	Only naftidrofuryl oxalate is considered a cost effective use of NHS resources for this indication. The Appraisal Committee concluded that though the Assessment Group's economic model included only one trial of naftidrofuryl, the ICER of the generic preparation at £6070 per QALY clearly dominated the ICERs for cilostazol and pentoxifylline, which were £50,740 and £54,800, respectively, and exceeded the threshold considered an acceptable use of NHS resources and any uncertainty regarding the ICER could be tolerated. The ICER for the branded preparation of naftidrofuryl is £11,060 per QALY and the committee advised that clinicians start with the least costly preparation. Inositol could not be included in the economic model, as the only trial included in the review did not show benefit for inositol relative to placebo and it was therefore inferred that inositol could not be cost effective in terms of the currently accepted threshold.	Comment noted.

Role*	Section	Comment	Response
NHS professional 3	5	We would expect realistic local acquisition costs to be incorporated into the HE analysis and the costing statement. Naftidrofuryl oxalate costs £8.10 for a pack of 84 capsules (excluding VAT BNF edition 60) a generic preparation is also available costing £5.30. The recommended dose is one to two 100mg capsules, three times daily. NICE estimates monthly costs of £8.80 to £17.89 for the branded preparation and £4.90 to £9.79 for the generic preparation. Other drugs: Cilostazol costs £35.31 per pack of 56x100mg tablets at the recommended dose of 100mg twice daily the average monthly cost is £38.26. Pentoxifylline costs £19.68 per pack of 90x400mg tablets the recommended dose is one tablet three times daily costing £19.90 per month (summary of product characteristics states that two tablets daily may prove sufficient in some patients). Inositol nicotinate costs £30.76 for a 100-tablet pack of 500mg tablets, or £51.03 for a 112-tablet pack of 750mg tablets at a dose of 3g daily (two 500 mg tablets three times a day) the average monthly cost is £56.14 (though 4g may be needed in some patients). (All costs excluding VAT BNF edition 60).	Comment noted.

Role*	Section	Comment	Response
NHS professional 3	6	The Assessment Group considered the trials to be of good quality, with comparable treatment groups between trials, maintenance of blinding and intention-to-treat analyses. However, the trials were almost all placebo-controlled with direct comparisons identified between only cilostazol and pentoxifylline. The Committee considered that the results of the network meta-analysis should be regarded with caution due to the wide credibility intervals indicating a high degree of uncertainty, heterogeneity between trials, the lack of differentiation between people who had and had not received supportive care and exercise therapy, and the inclusion of only one of five trials of naftidrofuryl. However, the Committee agreed that the relative benefits in terms of improvement in maximum walking were plausible given the empirical data. The other trials of naftidrofuryl were excluded on the grounds that they had not included comparable data on the outcome selected maximum walking distance. Trials of inositol nicotinate were also excluded from the meta-analysis for similar reasons.	Comment noted.