Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Final Protocol

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1. Title of the project:

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

2. Name of TAR team and 'lead'

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3. Plain English Summary

Peripheral arterial disease (PAD), also known as peripheral vascular disease, is a condition in which there is blockage of the arteries that carry blood to the legs and arms. The main cause is atherosclerosis. The major risk factors for developing PAD are smoking and diabetes mellitus. Other risk factors include hypertension, hyperlipidaemia, obesity, and a sedentary lifestyle. PAD can be asymptomatic (Fontaine Classification stage I) or symptomatic (Fontaine Classification stages II to IV). The commonest symptom of PAD is intermittent claudication (stage II), characterized by pain in the legs on walking that is relieved with rest. People with severe PAD experience pain at rest (stage III) and this can then progress to produce necrosis and gangrene (stage IV). Intermittent claudication increases with age and is more common in men than women. It has been estimated that approximately 20% of people aged from 55 to 75 years have evidence of PAD in the legs, and the prevalence of intermittent claudication has been estimated as 4.5% (Edinburgh Artery Study).[1] People with intermittent claudication are at increased risk of myocardial infarction and stroke.

A number of interventions are used for the conventional management of intermittent claudication. Treatment should be targeted at reducing the risk from cardiovascular events

such as smoking cessation, cholesterol lowering, glycaemic control, weight reduction and blood pressure control. Antiplatelet and statin therapy may be given as a long term prophylaxis of myocardial infarction and stroke. The management of claudication symptoms includes vasodilator therapy (cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate) and exercise therapy (supervised and unsupervised). For people with severe disability or deteriorating symptoms, angioplasty and bypass surgery may be considered as treatment options.

4. Decision problem

4.1 Purpose of the assessment

This review will assess the clinical and cost-effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication due to PAD in adults whose symptoms continue despite a period of conventional management. Conventional management usually involves 3 to 6 months of conservative treatment that would consist of risk modification, usually with a statin, aspirin, smoking cessation advice and advice to exercise (personal communication with Professor Jonathan Michaels).

4.2 Clear definition of the intervention

Cilostazol (Pletal, Otsuka Pharmaceuticals) is a phosphodiesterase III inhibitor. Cilostazol is a direct arterial vasodilator and it also inhibits platelet aggregation. It is administered orally. Cilostazol has a UK marketing authorisation for the improvement of the maximal and pain-free walking distances in patients with intermittent claudication, who do not have rest pain and who do not have evidence of peripheral tissue necrosis (peripheral arterial disease Fontaine stage II).

Naftidrofuryl oxalate (Praxilene, Merk Serono) is a peripheral vasodilator which selectively blocks vascular and platelet 5-hydroxytryptamine (5-HT2) receptors. Naftidrofuryl oxalate has a UK marketing authorisation for peripheral vascular disorders: intermittent claudication, night cramps, rest pain, incipient gangrene, trophic ulcers, Raynaud's Syndrome, diabetic arteriopathy and acrocyanosis.

Pentoxifylline (Trental 400, Sanofi-Aventis) is a peripheral vasodilator that is derived from methylxanthine. Pentoxifylline has a UK marketing authorisation for the treatment of peripheral arterial disease, including intermittent claudication and rest pain.

Inositol nicotinate (Hexopal, Genus Pharmaceuticals) is a peripheral vasodilator that is thought to work by slowing the release of nicotinic acid. Inositol nicotinate has a UK marketing authorisation for the symptomatic relief of severe intermittent claudication and Raynaud's phenomenon.

4.3 Relevant comparators

The interventions will be compared with each other. In addition, a range of management options for intermittent claudication due to PAD without vasodilator therapy are likely to be considered within the review. The precise definition of all of the comparators will be defined according to those comparators within the studies identified from the review.

4.4 Populations and relevant subgroups

The population will include people with intermittent claudication due to PAD whose symptoms continue despite a period of conventional management. If appropriate, and where evidence allows, subgroups will be considered according to cardiovascular risk factors and/or prior duration and content of therapy.

4.5 Key factors to be addressed

The review will aim to evaluate the following objectives:

1) Evaluate the clinical effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication due to PAD in adults whose symptoms continue despite a period of conventional management. Exact comparators will be established according to the identified studies from the review. Clinical outcomes considered will be maximal walking distance, pain-free walking distance, ankle brachial pressure index, vascular events (including interventions and requirement of hospitalisation), mortality, adverse effects of treatment and health-related quality of life.

2) Estimate the incremental cost effectiveness of vasodilator therapy.

3) Identify key areas for primary research.

4) Estimate the possible overall cost in England and Wales.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy

A comprehensive search will be undertaken to systematically identify clinical effectiveness literature concerning cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate within their licensed indications for the treatment of intermittent claudication in people with peripheral arterial disease.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

The following databases will be searched for published trials and systematic reviews: MEDLINE; MEDLINE in-Process and Other Non-Indexed Citations; EMBASE; Cochrane Library including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials; CINAHL; Web of Science Citation Index with Conference Proceedings and BIOSIS Previews. Searches for ongoing and recently completed research projects will be undertaken within the National Research Register and the metaRegister of Controlled Trials. Searches for unpublished research or research reported in the grey literature will also be undertaken within the Research Register and the metaRegister of Controlled Trials, in addition to contact with experts.

Searches will not be restricted by language, date or publication type. The MEDLINE search strategy is presented in Appendix 1. Any industry submissions, as well as any relevant systematic reviews will also be hand-searched in order to identify any further clinical trials.

5.2 *Inclusion criteria*

Inclusion criteria have been taken from the scope provided by NICE, outlined below.

Interventions

- cilostazol
- naftidrofuryl oxalate
- pentoxifylline
- inositol nicotinate

Population

- People with intermittent claudication due to peripheral arterial disease whose symptoms continue despite a period of conventional management

Comparator

- interventions compared with each other
- management of peripheral arterial disease without vasodilator therapy

Outcomes

- maximal walking distance
- pain-free walking distance
- ankle brachial pressure index
- vascular events (including interventions and requirement of hospitalisation)
- mortality
- adverse effects of treatment
- health-related quality of life

Study types

- randomised controlled trials (RCTs)

If no randomised controlled trials are identified for an intervention, nonrandomised controlled trials will be accepted. Systematic reviews will be checked for controlled trials that meet the inclusion criteria of this review.

5.3 *Exclusion criteria*

Studies based on animal models; preclinical and biological studies; editorials, opinion pieces; and reports published as meeting abstracts only where insufficient details are reported to allow inclusion. Studies which are only published in languages other than English are also likely to be excluded. Studies retrieved for full paper screening which are excluded will be listed in an appendix to the report with reasons for exclusion. Based on the above inclusion/exclusion criteria, study selection will be made by one reviewer, with involvement of a second reviewer when necessary.

5.4 *Data extraction and critical appraisal*

Data will be extracted with no blinding to authors or journal. Data will be extracted by one reviewer using a standardised form. Quality will be assessed according to criteria based on NHS CRD guidance for undertaking systematic reviews.[2] The quality assessment form for RCTs is shown in Appendix 2. The purpose of such quality assessment is to provide a narrative account of trial quality for the reader and, where meta-analysis is appropriate, inform potential exclusions from any sensitivity analysis. Further data extraction will include trial population, interventions, comparators and outcomes.

5.5 *Data synthesis*

Pre-specified outcomes will be tabulated and discussed within a descriptive synthesis. Where statistical synthesis is appropriate, meta-analysis will be conducted using fixed and random effect models, using RevMan software.[3] If sufficient trials are available, a sensitivity analysis will be undertaken to see if the removal of poor quality trials affects the results. In addition, a mixed treatment comparison using Bayesian evidence synthesis may be undertaken.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Studies relating to the costs and effects associated with management of intermittent claudication due to PAD will be identified using an economic search filter which will be integrated into the search strategy detailed in Section 5.1; this economic search filter is presented in Appendix 1. The inclusion criterion is any economic evaluation which meets the inclusion criteria outlined in Section 5.2 with regards to the population, intervention and comparator. Included studies will be synthesised within a qualitative analysis. The quality of economic literature will be assessed using a combination of key components of the British Medical Journal[4] checklist for economic evaluations together with the Eddy checklist on mathematical models[5] (see Appendix 3).

6.2 Methods for estimating costs and cost-effectiveness

It is expected that a *de novo* mathematical model may need to be developed to estimate the incremental cost-effectiveness ratio associated with cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate compared with management of intermittent claudication due to PAD without vasodilator therapy, in adults whose symptoms continue despite a period of conventional management. The model is likely to be developed within the computer software Excel. It will use efficacy data from the key RCTs identified through the systematic searches. Cost data for the economic model will be extracted from a variety of published sources. Costs will include the direct costs of the vasodilator therapy and its administration, as well as costs of adverse events. Direct savings due to the avoidance of additional treatment costs which would have been incurred as a result of vascular events in the absence of vasodilator therapy will be incorporated.

The final outcome measures estimated within the model will depend on the available evidence, but are likely to include cost per life year gained (LYG) and cost per quality-adjusted life year (QALY) gained. It is hoped that suitable quality of life data will be identified from the literature. In the absence of quality of life data, the model may use indirect evidence on quality of life from alternative sources. If it were not feasible to estimate the cost

per QALY gained, this would be clearly specified and justified, and the likely implications would, as far as possible, be quantified.

The time horizon of our analysis will be a patient's lifetime in order to reflect the chronic nature of the disease. The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%. Sensitivity analyses, including probabilistic sensitivity analysis (PSA), will be undertaken to assess the impact of uncertain parameters upon the model results. Results of the PSA will be shown graphically within cost-effectiveness acceptability curves. Expected value of perfect information (EVPI) will also be estimated. If resources allow, expected value of partial perfect information (EVPPI) may also be considered.

7. Handling the company submission(s)

The TAR team will be happy to consider any evidence submitted by the manufacturers/ sponsors if received by 20th July 2010. It may not be possible to consider data arriving after this date. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing de-novo modelling.

Any 'commercial in confidence' data taken from a company submission will be highlighted and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Cic data will be in turquoise and aic data will be in yellow.

8. Competing interests of authors

There are no competing interests.

9. Appendices

Appendix 1: Search Strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1 Intermittent Claudication/
2 claudication.tw.
3 1 or 2
4 exp Peripheral Vascular Diseases/
5 (peripheral adj arterial adj disease$).tw.
6 (peripheral adj vascular adj disease$).tw.
7 (atherosclero$ and (PAD or PVD)).tw.
8 ((arterial adj disease$) and (PAD or PVD)).tw.
9 or/4-8
10 Atherosclerosis/dt, th [Drug Therapy, Therapy]
11 Vascular Diseases/dt, th [Drug Therapy, Therapy]
12 Vasodilator Agents/
13 vasodilator$.tw.
14 Platelet Aggregation Inhibitors/
15 (platelet adj aggregation adj inhibitor$).tw.
16 Phosphodiesterase Inhibitors/
17 (phosphodiesterase adj inhibitor$).tw.
18 Tetrazoles/tu [Therapeutic Use]
19 or/10-18
20 3 and 9 and 19
21 cilostazol$.tw.
22 (pletal or pletaal).tw.
23 OPC-13013.tw.
24 73963-72-1.rn.
25 or/21-24
26 3 and 25
27 9 and 25
28 Nafronyl/
29 naftidrofuryl$.tw.
30 naphtidrofuryl.tw.
31 (nafronyl or naftifurin).tw.

32 praxilene.tw.
33 (dusodril or iridus).tw.
34 3200-06-4.rn.
35 or/28-34
36 3 and 35
37 9 and 35
38 Pentoxifylline/
39 pentoxifylline.tw.
40 trental.tw.
41 oxpentifylline.tw.
42 (pentoxil or pentofin).tw.
43 bl-191.tw.
44 6493-05-6.rn.
45 or/38-44
46 3 and 45
47 9 and 45
48 Nicotinic Acids/
49 (inositol adj (nicotinate or hexanicotinate)).tw.
50 (inositol adj niacinate).tw.
51 hexopal.tw.
52 (dilexpal or mesotal or palohex or hexanicotol or esantene or hexanicit or linodil or mesonex or dilcit).tw.
53 6556-11-2.rn.
54 or/48-53
55 3 and 54
56 9 and 54
57 26 or 36 or 46 or 55
58 27 or 37 or 47 or 56
59 57 or 58
60 20 or 59

Electronic databases to be searched will include MEDLINE; MEDLINE in-Process and Other Non-Indexed Citations; EMBASE; Cochrane Library including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials; CINAHL; Web of Science Citation Index with Conference Proceedings; BIOSIS Previews; National Research Register and the metaRegister of Controlled Trials.

The above search strategy will be adapted across multiple databases. Specific MesH headings and free-text terms of the four interventions have been identified and will be combined with intermittent claudication (21-59). Broad intervention terms are also included in the strategy and will be combined with intermittent claudication and peripheral arterial disease (10-20). No date or language restrictions will be applied.

For the clinical effectiveness searches, a filter will be applied to retrieve randomized controlled trial studies. Additional searches will be carried out on the adverse effects and the quality of life outcomes of each intervention.

RCT search filter for Ovid MEDLINE(R)

61 Randomized controlled trials as Topic/
62 Randomized controlled trial/
63 Random allocation/
64 Double blind method/
65 Single blind method/
66 Clinical trial/
67 Exp Clinical Trials as Topic/
68 Or/61-67
69 (clinic$ adj trial$).tw.
70 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
71 Placebos/
72 Placebo$.tw.
73 Randomly allocated.tw.
74 (allocated adj2 random).tw.
75 Or/69-74
76 8 or 15
77 Case report.tw.
78 Letter/
79 Historical article/
80 or/77-79
81 76 not 80
82 81 and 1-60 from the searches above

For the cost-effectiveness searches, an economic search filter will be integrated into the search strategy above.

Economic search filter for Ovid MEDLINE(R)

61 exp "costs and cost analysis"/
62 economics/
63 exp economics, hospital/
64 exp economics, medical/
65 economics, nursing/
66 exp models, economic/
67 economics, pharmaceutical/
68 exp "fees and charges"/
69 exp budgets/
70 budget$.tw
71 ec.fs
72 cost$.ti
73 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab
74 (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti
75 (price$ or pricing$).tw
76 (financial or finance or finances or financed).tw
77 (fee or fees).tw
78 (value adj2 (money or monetary)).tw
79 quality-adjusted life years/
80 (qaly or qalys).af.
81 (quality adjusted life year or quality adjusted life years).af.
82 or/61-81
83 82 and 1-60 from the searches above

Additional searches such as cardiovascular events to inform the decision-analytic model where required in the course of the project, will be carried out through consultation between the information specialist and the MTA team.

Appendix 2: Randomised controlled trial quality assessment scale (adapted from NHS CRD (2009)[2]

	Yes/No/ Unclear
Was the method used to generate the allocation sequence to treatment groups adequate?	
Was the allocation of treatment concealed adequately?	
Were the treatment groups comparable at baseline?	
Were clinicians, participants and outcome assessors blind to treatment allocation?	
Were participants analysed in their allocated treatment groups, in accordance with the intention-to-treat principle?	
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	
Were there any imbalances in drop-outs between groups? If so, were these adjusted for in analyses?	
Is there any evidence of selective reporting of outcomes (i.e. that the authors measured more outcomes than reported)?	

Appendix 3: Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluations[4] together with the Eddy checklist on mathematical models employed in technology assessments.[5]

Reference ID		
Title		
Authors		
Year		
Modelling assessments should include:		Yes/No
1	A statement of the problem.	
2	A discussion of the need for modelling vs. alternative methodologies.	
3	A description of the relevant factors and outcomes.	
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. *Note: n=number of health states within sub-model*	
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence.	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data.	
7	A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis.	
8	The results derived from applying the model for the base case.	
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.	
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect.	
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity.	
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results.	
13	A description of research in progress that could yield new data that could alter the results of the analysis.	

REFERENCES

1. Fowkes, F. G. R., Housley, E., Cawood, E. H. H., MacIntyre, C. C. A., Ruckley, C. V., and Prescott, R. J. Edinburgh Artery Study: Prevalence of Asymptomatic and Symptomatic Peripheral Arterial Disease in the General Population. *International Journal of Epidemiology* 1-6-1991; **20** 384-392.

2. Centre for Reviews and Dissemination Systematic reviews: CRD's guidance for undertaking reviews in health care. 2009; **3rd edition**

3. Cochrane Collaboration, Oxford UK RevMan Version 5, The Cochrane Review Manager; The Cochrane Collaboration. 2008;

4. Drummond, M and Jefferson, TO Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996; **313** 275-283.

5. Eddy, DM The role of mathematical modeling. in Assessing medical technology. *Technology Assessment* 1985;144-154.