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

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

Ordering information

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- The NICE guidance (this document).
- A quick reference guide – the recommendations.
- ‘Understanding NICE guidance’ – a summary for patients and carers.
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or ‘Understanding NICE guidance’, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N2555 (quick reference guide)
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National Institute for Health and Clinical Excellence

MidCity Place
71 High Holborn
London WC1V 6NA

www.nice.org.uk

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1 Guidance

- 1.1 Naftidrofuryl oxalate is recommended as an option for the treatment of intermittent claudication in people with peripheral arterial disease for whom vasodilator therapy is considered appropriate after taking into account other treatment options. Treatment with naftidrofuryl oxalate should be started with the least costly licensed preparation.
- 1.2 Cilostazol, pentoxifylline and inositol nicotinate are not recommended for the treatment of intermittent claudication in people with peripheral arterial disease.
- 1.3 People currently receiving cilostazol, pentoxifylline and inositol nicotinate should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 Clinical need and practice

- 2.1 Peripheral arterial disease, also known as peripheral vascular disease, is a condition in which arteries that carry blood to the legs or arms are narrowed or blocked. The main cause of peripheral arterial disease is atherosclerosis. The major risk factors for peripheral arterial disease are smoking, diabetes mellitus and pre-existing cardiovascular disease. Other factors include increasing age, male sex, ethnicity, hypertension, hypercholesterolaemia, renal insufficiency and a sedentary lifestyle
- 2.2 The Fontaine scheme classifies four stages of peripheral arterial disease. Peripheral arterial disease can be asymptomatic (Fontaine stage I) or symptomatic (Fontaine stages II–IV). The most common symptom of peripheral arterial disease is intermittent claudication (Fontaine stage II), which is characterised by pain in the legs or buttocks that occurs with exercise and is relieved with rest. Two further stages exist: pain in the extremities at rest (ischaemic rest pain, Fontaine stage III) and necrosis and gangrene (Fontaine stage IV).

- 2.3 The pain associated with intermittent claudication occurs because of a lack of oxygen in the leg muscles owing to the impaired blood supply. Rest normalises blood flow and relieves the pain. Intermittent claudication is most commonly associated with disease in the femoropopliteal segment of the arterial circulation. Peripheral arterial disease can also be present at the aorto–iliac level causing pain in the thigh, hip or buttock. Peripheral arterial disease can also cause foot pain. Around 20% of people aged 55–75 years have evidence of peripheral arterial disease in the legs and a quarter of these have symptoms.
- 2.4 Intermittent claudication worsens people’s quality of life because it restricts their mobility. People with peripheral arterial disease, and specifically with intermittent claudication, are at increased risk of myocardial infarction and stroke. Additionally, people with intermittent claudication are at higher risk from cardiovascular mortality than people with asymptomatic peripheral arterial disease.
- 2.5 The diagnosis of intermittent claudication includes a clinical history that assesses the presence and character of the pain. A clinician may also measure a patient’s ankle-brachial pressure index, that is, the ratio of the blood pressure in the lower leg to the blood pressure in the arm at rest. A value of 0.9 indicates disease, and high values (that is, greater than 1.3) may reflect arterial stiffening associated with disease.
- 2.6 Evaluating the presence and progression of disease takes into account symptoms and signs (for example, the development of ischaemic ulcers). As an objective measure, walking on a treadmill, either at a fixed speed and slope, or a fixed speed and increasing slope, determines how far a patient can walk before developing claudication pain and how far a patient can walk with pain before having to stop.

2.7 A number of interventions are used to manage intermittent claudication. Stopping smoking and increasing exercise can help reduce symptoms of claudication. People are more likely to benefit from supervised exercise programmes than from unsupervised exercise. Vasoactive drugs including cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate have marketing authorisations for the symptomatic relief of intermittent claudication and are considered in this appraisal. Angioplasty (that is, mechanical widening of the blood vessel) or other revascularisation (for example, arterial bypass) may be undertaken for people whose symptoms continue despite treatment. To reduce the risk of a heart attack or stroke, interventions include helping patients stop smoking, lowering cholesterol, controlling blood pressure, offering aspirin, and, in people with diabetes, controlling glycaemia.

3 The technologies

3.1 Cilostazol (Pletal, Otsuka Pharmaceuticals) is an oral phosphodiesterase III inhibitor. Cilostazol is a direct arterial vasodilator and it also inhibits platelet aggregation. 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'. Cilostazol is contraindicated in people with severe renal impairment (creatinine clearance of 25 ml/min or lower), moderate or severe hepatic impairment, congestive heart failure and pregnancy. Cilostazol is also contraindicated in people with any known predisposition to bleeding or with any history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopic beats. For full details of side effects and contraindications see the summaries of product characteristics.

3.2 Cilostazol is available as a 50 or 100 mg tablet at a cost of £35.31 for a 56-tablet pack (price for either dose, excluding VAT; 'British national formulary' [BNF] edition 60). The recommended dose is

100 mg twice daily. Therefore, assuming 100 mg tablets are used, the average monthly cost is £38.26. Costs may vary in different settings because of negotiated procurement discounts.

3.3 Naftidrofuryl oxalate (Praxilene, Merk Serono) is an oral peripheral vasodilator that selectively blocks vascular and platelet 5-hydroxytryptamine 2 (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'. Naftidrofuryl oxalate is contraindicated in people with a history of hyperoxaluria or recurrent calcium-containing stones. For full details of side effects and contraindications see the summary of product characteristics.

3.4 Naftidrofuryl oxalate is available as a branded preparation of 100 mg capsules at a cost of £8.10 for an 84-capsule pack (excluding VAT; BNF edition 60). Generic preparations are also available at a cost of £5.30 (excluding VAT; BNF edition 60), and since January 2011 at a cost of £4.52 (excluding VAT; BNF edition 61) for a 100 mg 84-capsule pack. The recommended dose is one or two 100 mg capsules three times daily. Therefore, for the branded preparation the average monthly cost is £8.80 assuming three 100 mg capsules daily or £17.89 assuming six 100 mg capsules daily. For the generic preparation (that is at a cost of £5.30, excluding VAT; BNF edition 60) the average monthly cost is £4.90 for three 100 mg capsules daily or £9.79 assuming six 100 mg capsules daily. Costs may vary in different settings because of negotiated procurement discounts.

3.5 Pentoxifylline (Trental 400, Sanofi-Aventis) is an oral peripheral vasodilator derived from methylxanthine. Pentoxifylline has a UK marketing authorisation for the 'treatment of peripheral vascular disease, including intermittent claudication and rest pain'. Pentoxifylline is contraindicated in people with cerebral

haemorrhage, extensive retinal haemorrhage, acute myocardial infarction and severe cardiac arrhythmias. For full details of side effects and contraindications see the summary of product characteristics.

- 3.6 Pentoxifylline is available as a 400 mg tablet at a cost of £19.68 for a 90-tablet pack (excluding VAT; BNF edition 60). The recommended dose is one tablet three times daily. Therefore, the average monthly cost is £19.90. However, the summary of product characteristics states that two tablets daily may prove sufficient in some patients, particularly for maintenance therapy. Costs may vary in different settings because of negotiated procurement discounts.
- 3.7 Inositol nicotinate (Hexopal, Genus Pharmaceuticals) is an oral peripheral vasodilator that slows the release of nicotinic acid. Inositol nicotinate has a UK marketing authorisation for 'the symptomatic relief of severe intermittent claudication and Raynaud's phenomenon'. Inositol nicotinate is contraindicated in people who have suffered a recent myocardial infarction or are in the acute phase of a stroke. For full details of side effects and contraindications see the summaries of product characteristics.
- 3.8 Inositol nicotinate is available as a 500 mg tablet at a cost of £30.76 for a 100-tablet pack. It is also available as a 750 mg tablet at a cost of £51.03 for a 112-tablet pack (excluding VAT; BNF edition 60). The recommended dose is 3 g daily (that is, two 500 mg tablets three times a day), increased to 4 g daily if necessary. The average monthly cost, assuming two 500 mg tablets three times a day, is £56.14. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 *Clinical effectiveness*

4.1.1 The Assessment Group conducted a systematic review of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate within their licensed indications for the treatment of intermittent claudication in people with peripheral arterial disease whose symptoms continue despite conventional management. The Assessment Group identified 26 randomised controlled trials, including placebo-controlled trials, for all four of the vasoactive drugs. The only head-to-head comparison was between cilostazol and pentoxifylline. The Assessment Group stated that the quality of the trials was generally good: treatment groups within trials were comparable, blinding was maintained and trials presented intention-to-treat analyses.

Cilostazol: maximum walking distance

4.1.2 The Assessment Group identified 11 randomised controlled trials of cilostazol 200 mg compared with placebo. In addition, three randomised controlled trials of cilostazol 200 mg compared with pentoxifylline 1200 mg and one randomised controlled trial of cilostazol 200 mg (with or without supervised exercise) compared with usual care (with or without supervised exercise) were identified. The duration of treatment of the randomised controlled trials ranged from 12 weeks to 24 weeks; 6 had a treatment duration of 24 weeks, 1 of 16 weeks and 3 of 12 weeks. The outcomes included in the trials were maximum walking distance (before having to stop because of pain), pain-free walking distance (before developing claudication pain), ankle brachial pressure index, cardiovascular events, mortality, adverse events and health-related quality of life. The mean baseline age of the participants across the trials ranged from 63 to 67 years. The number of

participants in the trials ranged from 81 to 1435. Of the 11 randomised controlled trials, two recruited patients from the UK (n = 38 and 106).

- 4.1.3 Of the 11 trials of cilostazol 200 mg compared with placebo, ten reported the outcome of maximum walking distance. Of these, seven showed that cilostazol improved maximum walking distance to a statistically significant degree compared with placebo. Studies reported the mean improvement in maximum walking distance either in percentages or as an absolute value. Two of the studies reported percentages; one of these reported 161.7% mean improvement for the group randomised to cilostazol and 79% mean improvement for the group randomised to placebo. The other reported a 30.5% improvement for the group randomised to cilostazol and a 9.3% worsening for the group randomised to placebo. The other studies reported mean improvement in metres. The individual results for the groups randomised to cilostazol compared with placebo respectively were: 76.2 metres versus 21.1 metres, 107 metres versus 65 metres, 129.1 metres versus 26.8 metres, 96.4 metres versus 31.4 metres and 72.7 metres versus 25.8 metres. Three trials that compared cilostazol with pentoxifylline reported the outcome of maximum walking distance. Only one of these trials found a statistically significant improvement in maximum walking distance for cilostazol compared with pentoxifylline (mean maximum walking distance improved by 107 metres with cilostazol compared with 64 metres with pentoxifylline [$p = 0.0002$]). The other two studies showed no significant difference between cilostazol and pentoxifylline. One trial compared people randomised to cilostazol (with or without supervised exercise) with usual care (with or without supervised exercise). The results of this trial showed that all treatment groups improved regardless of randomisation, but that greater improvement occurred when cilostazol was added to supervised exercise (mean ratio – change in maximum walking

distance: cilostazol plus exercise 2.58, cilostazol without exercise 1.69, usual care plus exercise 1.45, usual care without exercise 1.09, $p = 0.005$).

Cilostazol: pain-free walking distance

- 4.1.4 For cilostazol 200 mg compared with placebo, 10 trials reported the outcome of pain-free walking distance. Of these, five trials showed that cilostazol improved pain-free walking distance to a statistically significant degree compared with placebo. In two of the trials, the mean (absolute) difference in metres was reported. The results for distances in people randomised to cilostazol compared with placebo respectively were 94 metres versus 57 metres, and 68 metres versus 23 metres. One trial showed a 31.7% improvement in people randomised to cilostazol compared with a 2.5% worsening with placebo. One trial reported only a p value ($p < 0.05$) and another one showed a net improvement of 22% between groups, with the comparison favouring cilostazol.
- 4.1.5 Three trials of cilostazol compared with pentoxifylline reported the outcome of pain-free walking distance, of which one found a statistically significant improvement for the group randomised to cilostazol compared with pentoxifylline (mean pain-free walking distance improved by 94 metres for those patients in the cilostazol group compared with 74 metres for those in the pentoxifylline group [$p = 0.02$]). The results of the one trial comparing cilostazol (with or without supervised exercise) with usual care (with or without supervised exercise) showed an improvement in pain-free walking distance for all four randomisation groups (that is, cilostazol with supervised exercise, cilostazol without supervised exercise, usual care with supervised exercise and usual care without supervised exercise). However, there was no statistically significant effect of cilostazol when added to supervised exercise or usual care (mean ratio – change in maximum walking distance: cilostazol plus supervised exercise 3.84, cilostazol without supervise exercise

3.34, usual care plus supervised exercise 2.22, usual care without supervised exercise 1.23).

Naftidrofuryl oxalate: maximum walking distance and pain-free walking distance

- 4.1.6 The Assessment Group identified four randomised controlled trials of naftidrofuryl oxalate 600 mg compared with placebo and one randomised controlled trial of naftidrofuryl oxalate 300 mg compared with placebo. The duration of treatment of the trials ranged from 12 weeks to 24 weeks; three were 24 weeks long and two were 12 weeks long. The outcomes included in these studies were maximum walking distance, pain-free walking distance, ankle brachial pressure index, cardiovascular events, mortality, adverse events and health-related quality of life. The mean baseline age of the participants receiving naftidrofuryl oxalate in three of the trials ranged from 58 to 67 years. Baseline age of participants in the remaining trials was not reported in the assessment report. The number of participants in the trials ranged from 50 to 754. Only one randomised controlled trial recruited UK patients (n = 50).
- 4.1.7 Two trials of naftidrofuryl oxalate 600 mg compared with placebo included the outcome of maximum walking distance. One of the trials showed a statistically significant improvement in maximum walking distance for naftidrofuryl oxalate compared with placebo ($p < 0.001$). In this trial, the maximum walking distance of patients randomised to naftidrofuryl oxalate was improved by 158.7 metres compared with 28.1 metres for placebo. For the outcome of pain-free walking distance, five trials that compared naftidrofuryl oxalate with placebo reported this outcome. Four of the trials showed a statistically significant improvement in pain-free walking distance with naftidrofuryl oxalate compared with placebo (mean differences in metres were 204.0, 158.2, 201.4 and 93.0 for those in the naftidrofuryl oxalate groups compared with 51.0, 29.9, 98.0 and 36.0 for those in the placebo group respectively).

Pentoxifylline: maximum walking distance and pain-free walking distance

- 4.1.8 The Assessment Group identified nine randomised controlled trials of pentoxifylline 1200 mg compared with placebo. The treatment durations ranged from 8 weeks to 52 weeks (one had a treatment duration of 52 weeks, six of 24 weeks, and two of 8 weeks). The outcomes included in these trials were maximum walking distance, pain-free walking distance, ankle brachial pressure index, cardiovascular events (and cardiovascular events leading to withdrawal), mortality, adverse events and health-related quality of life. The mean baseline age of the participants receiving pentoxifylline ranged from 59 to 68 years. The number of participants in the trials ranged from 24 to 524. None of the nine randomised controlled trials recruited patients from the UK.
- 4.1.9 Of the nine trials of pentoxifylline 1200 mg, eight reported the outcome of maximum walking distance. Two of the eight trials showed a statistically significant improvement in maximum walking distance for the group randomised to pentoxifylline compared with placebo. One of these trials reported a 13.9% improvement for people in the pentoxifylline group compared with 3.3% improvement for those in the placebo group. The other trial reported a mean difference improvement of 136 metres for people in the pentoxifylline group compared with 6 metres for those in the placebo group.
- 4.1.10 Seven trials that compared pentoxifylline 1200 mg with placebo reported the outcome of pain-free walking distance. Two trials showed a statistically significant improvement in pain-free walking distance in people randomised to pentoxifylline compared with placebo. One of these reported a mean difference in improvement of 74 metres with pentoxifylline compared with 57 metres with placebo ($p = 0.07$). The other trial reported a 47% improvement (geometric mean) for the group randomised to pentoxifylline

compared with 26% for the group randomised to placebo (2-sided $p = 0.042$).

Inositol nicotinate: maximum walking distance

4.1.11 The Assessment Group identified three randomised controlled trials of inositol nicotinate 4 g compared with placebo. The duration of treatment in each of the trials was 12 weeks. The outcomes included were pain-free walking paces, maximum walking distance, ankle brachial pressure index, time to claudication, cardiovascular events, mortality and adverse events. The mean baseline age of the participants receiving inositol nicotinate ranged from 61 to 68 years. The number of participants in the trials ranged from 80 to 123. One trial reported the outcome of maximum walking distance. The results of this trial showed no statistically significant differences between the groups given inositol nicotinate and placebo. None of the three trials reported pain-free walking distance.

Assessment Group meta-analyses

4.1.12 The Assessment Group conducted a meta-analysis of the data for maximum walking distance for cilostazol relative to placebo, reanalysing results from a previous Cochrane review. A random effects meta-analysis of the change in walking distance from baseline showed that treatment with cilostazol compared with placebo resulted in an increase of 52.27 metres in absolute walking distance (95% credible interval [interval estimate based on Bayesian techniques] 24.93 to 86.57).

4.1.13 The Assessment Group also undertook a network meta-analysis of the data for maximum walking distance for the overall comparison of treatment options. The objective of the meta-analysis was to estimate the effect of treatment for each drug in comparison with placebo, and, if possible, compared with each other. This consisted of an analysis of the change from baseline to end of study in log mean maximum walking distance (log metre) from ten out of the 26 trials (seven two-arm, and three three-arm 24 week trials

leading to 16 comparisons) that the Assessment Group had identified for cilostazol, naftidrofuryl oxalate and pentoxifylline. Reasons for excluding studies included that studies were shorter than 24 weeks in duration, were not written in English, lacked endpoints (for example, maximum walking distance or pain-free walking distance), did not report results in a way that allowed comparison of results across trials, used inappropriately low drug dosages, were secondary analyses, used an unlicensed route of administration (that is, intravenous pentoxifylline), included people with disease classified as high Fontaine stages (for example gangrene), or included people who were receiving concurrent revascularisation. The Assessment Group stated that inositol nicotinate was not included in the meta-analysis because the studies lacked 24-week data or data reported in the trials were not suitable for inclusion (there was no information on percentage change from baseline and no information on maximum walking distance or pain-free walking distance). The Assessment Group transformed the data on maximum walking distance to the logarithm scale to produce a scale on which the treatment effects could be assumed to be linear.

- 4.1.14 The random effects meta-analysis of the change from baseline to end of study in log mean maximum walking distance showed that the greatest increase compared with placebo was for naftidrofuryl (60.3%), followed by cilostazol (24.6%) and pentoxifylline (10.6%). The 95% credible intervals for naftidrofuryl oxalate and cilostazol suggested that there was an increase in the percentage change from baseline walking distance when compared with placebo, although there was some uncertainty about the true effect. Variation between studies was moderate, suggesting that the treatment effect varied depending on the characteristics of the study.

4.1.15 The Assessment Group also undertook a network meta-analysis of the data for pain-free walking distance for the overall comparison of treatment options. This included the same trials as the meta-analysis of maximum walking distance. The random-effects meta-analysis of the change from baseline in log pain-free walking distance showed that treatment with naftidrofuryl oxalate compared with placebo had the greatest effect (64.2%) followed by cilostazol (13.4%) and pentoxifylline (9.2%). The 95% credible interval suggested that treatment with naftidrofuryl oxalate and cilostazol compared with placebo resulted in increases in the percentage change from baseline pain-free walking distance, although there was some uncertainty about the true effect. The variation between studies was moderate, and probably reflected differences in the design of the studies.

Adverse events

4.1.16 The reporting of adverse event data varied across the trials. A number of trials reported only the adverse events that led patients to stop taking the drug. Other studies reported no clear clinical criteria for adverse events. Only two trials that reported adverse events had a follow-up of more than 24 weeks. These factors meant the Assessment Group could not undertake a meta-analysis of adverse events.

4.1.17 Of the 26 trials included in the Assessment Group's systematic review, 18 reported on deaths (nine comparing cilostazol with placebo, two comparing cilostazol with pentoxifylline, one comparing naftidrofuryl oxalate with placebo, five comparing pentoxifylline with placebo and one comparing inositol with placebo). Follow-up was relatively short and no significant differences in mortality rates were reported between any treatment groups.

4.1.18 Cardiovascular events were reported in 18 of the 26 trials identified by the Assessment Group (eight comparing cilostazol with placebo,

which were included in a published analysis of adverse events; one comparing naftidrofuryl oxalate with placebo; six comparing pentoxifylline with placebo; and three comparing inositol nicotinate with placebo). No significant differences in cardiovascular events were observed between any treatment groups.

4.1.19 With respect to other adverse events, eight of the trials comparing cilostazol with placebo were included in a published analysis of adverse events. The results showed a higher frequency of headaches, diarrhoea, peripheral oedema and palpitations in the cilostazol groups than in the placebo groups. In three trials that compared cilostazol with pentoxifylline, similar rates of serious adverse events and adverse events were reported in both treatment groups.

4.1.20 In the studies that compared pentoxifylline with placebo, similar rates of adverse and serious adverse events were reported in both groups. Non-serious adverse events were mostly headaches or gastrointestinal complaints.

4.1.21 In the studies that compared 600 mg or 300 mg of naftidrofuryl oxalate with placebo the rates of adverse events and serious adverse events were similar between treatment groups.

4.1.22 Four trials that compared inositol nicotinate with placebo reported only adverse events that led to withdrawal from trials, and these were similar between treatment groups and mostly related to difficulty in swallowing or gastrointestinal problems.

4.2 Cost effectiveness

4.2.1 None of the five manufacturers submitted cost-effectiveness evidence or an economic model.

4.2.2 The Assessment Group developed a de novo Markov economic model to estimate the cost effectiveness of the vasoactive drugs cilostazol, naftidrofuryl oxalate and pentoxifylline compared with

each other and with no vasoactive drugs. The Assessment Group stated that it excluded inositol nicotinate from the main analysis because it had not been possible to include it in the meta-analyses of maximum walking distance and pain-free walking distance. Instead, the cost effectiveness of inositol nicotinate was assessed in a threshold analysis to determine how effective (in terms of quality-adjusted life years [QALYs]) inositol nicotinate would have to be to consider it a cost-effective use of NHS resources.

4.2.3 The model had three distinct health states: treatment with one of the four drugs under evaluation, no treatment (in which patients received none of the four drugs or had received the drug but had discontinued it) and death. The Assessment Group did not include a state reflecting progression of disease in the economic model, because the drugs under evaluation relieve symptoms and are not assumed to affect disease progression or the incidence of cardiovascular events. The model assumed that treatment with vasoactive drugs improved quality of life. It also assumed that a person could stop drug treatment because of adverse events, deaths or for other reasons of non-adherence. The model assumed no further benefit once drug treatment was stopped. The model had a cycle of 1 week and a lifetime horizon.

4.2.4 The population included in the economic model comprised people with peripheral arterial disease, whose intermittent claudication had been stable for at least 3 months and whose symptoms continued despite conventional management including exercise and stopping smoking. The Assessment Group chose 66 years as the average age of patients with intermittent claudication based on one of the trials comparing cilostazol with placebo, which had the longest follow-up period and the largest sample size of all randomised controlled trials included in the Assessment Group's systematic review. The economic model did not distinguish between people followed in primary and secondary care. An exploratory subgroup

analysis was presented for people who have more severe intermittent claudication who might have angioplasty after stopping one of the vasoactive drugs.

- 4.2.5 Only two randomised controlled trials (both for cilostazol) included in the Assessment Group's systematic review provided quality of life data from SF-36. The Assessment Group converted these to utility values using a published algorithm. The Assessment Group requested patient-level or summary SF-36 data from the authors of both trials in which the SF-36 questionnaire was used. The Assessment Group aimed to use the data to determine a relationship between the change in mean walking distance and the change in SF-36 to the change in utility scores, which it could then use to estimate the utility gain for each of the four vasoactive drugs. The authors of one trial comparing cilostazol with no vasoactive treatment provided a complete set of patient-level data (n = 106) for mean walking distance and SF-36 scores.
- 4.2.6 The Assessment Group estimated utility values using a published algorithm for converting SF-36 data at week 0 and 24. The patient-level data were used to test for a correlation between the change in maximum walking distance and the change in utility values from week 0 to week 24. The Assessment Group then used a linear regression model to estimate the absolute changes in utility values from the absolute change in the maximum walking distance on the logarithm scale during the period of the randomised controlled trial. The Assessment Group applied a regression model to all four treatments and to no vasoactive treatment to estimate the absolute changes in utility values given a certain change in mean walking distance from week 0 to week 24. The Assessment Group also estimated a mean baseline (that is, at week 0) utility value of 0.4838 using the patient-level data.
- 4.2.7 The Assessment Group applied age-adjusted utility values for the general population (that is, for people unlikely to have intermittent

claudication) from a published algorithm. The Assessment Group then adjusted these utility values for the general population downwards to account for the lower average utility associated with intermittent claudication. The Assessment Group estimated that at 24 weeks the mean utility of a person who had not been treated with a vasoactive drug was 0.4873, compared with values of 0.4973 for cilostazol, 0.5088 for naftidrofuryl oxalate and 0.4919 for pentoxifylline.

- 4.2.8 The Assessment Group assumed that mortality rates did not differ whether a patient received treatment or not, or by which treatment a patient received, because vasoactive treatment provides only symptomatic relief and is unlikely to affect the progression of peripheral vascular, or other cardiovascular, disease. The Assessment Group obtained the death rates in the general population from the life tables for England and Wales (Office for National Statistics, 2008). The mortality of the general population was multiplied by a factor reflecting the increased mortality for patients with intermittent claudication (relative risk 1.6) based on a study of the risk of mortality and cardiovascular disease associated with a low ankle-brachial pressure index.
- 4.2.9 The Assessment Group based the costs of the drugs on the drug tariff of October 2010. If there was more than one licensed dose, the Assessment Group used the cost associated with the doses used in the trials included in its systematic review. In the base case, the model used the cost of generic naftidrofuryl oxalate. In sensitivity analyses, the Assessment Group explored the impact on the incremental cost-effectiveness ratio (ICER) of using the price of the branded preparation (see 4.2.11). The Assessment Group assumed that no difference existed in the costs of diagnosis and frequency of follow-up visits for people treated with vasoactive drugs compared with people not treated with vasoactive drugs.

- 4.2.10 The base-case results suggested that cilostazol compared with no vasoactive drug provided 0.019 additional QALYs at an additional cost of £964, resulting in an ICER OF £50,737 per QALY gained. Naftidrofuryl oxalate compared with no vasoactive drug provided 0.049 additional QALYs at an additional cost of £298, resulting in an ICER of £6070 per QALY gained. Pentoxifylline was estimated to have the smallest QALY gains (0.009) compared with no vasoactive drug at an additional cost of £493, resulting in an ICER of £54,777 per QALY gained. Overall, the results showed that both pentoxifylline and cilostazol are dominated by naftidrofuryl oxalate, which resulted in the largest total QALY gain and was associated with the lowest additional costs.
- 4.2.11 The Assessment Group undertook one-way sensitivity analyses using the following assumptions: that the utility value does not drop if the drug is stopped after 24 weeks; alternative baseline utility values; an alternative cost for naftidrofuryl oxalate (the price of the branded preparation); shorter time horizon; alternative starting age (55 years) and alternative rates of discontinuation. The results of the sensitivity analyses indicated that the ICERs of naftidrofuryl oxalate were relatively insensitive to different baseline utility values, alternative starting ages, and alternative long-term discontinuation rates. However, the ICER of naftidrofuryl oxalate decreased to £1538 per QALY gained when the effectiveness associated with the vasoactive drugs was assumed to continue over a patient's lifetime when they stop the drug after 24 weeks. The Assessment Group also explored the impact on the ICER of using the price of the branded preparation of naftidrofuryl oxalate in a sensitivity analysis, which increased the ICER to £11,060 per QALY gained. In all of the sensitivity analyses performed by the Assessment Group, both cilostazol and pentoxifylline were dominated or extendedly dominated by naftidrofuryl oxalate.

- 4.2.12 The Assessment Group provided threshold analyses that estimated the number of QALYs each drug would have to generate to result in ICERs below £20,000 and £30,000 per QALY gained. These analyses showed that naftidrofuryl oxalate needed the smallest QALY gains compared with no vasoactive treatment of 0.015 and 0.010. Pentoxifylline needed QALY gains of 0.025 and 0.016, cilostazol needed QALY gains of 0.048 and 0.032, and inositol nicotinate needed QALY gains of 0.085 and 0.056 respectively.
- 4.2.13 In response to consultation on the appraisal consultation document, the manufacturer of cilostazol expressed concerns that the network meta-analyses undertaken by the Assessment Group may have overestimated the clinical benefit of naftidrofuryl oxalate, and highlighted the exclusion of one of three excluded trials of naftidrofuryl oxalate from the network-meta analyses. The 24 week trial highlighted by the manufacturer was published in 1986 and compared naftidrofuryl oxalate 600 mg (n = 64) with placebo (n = 54). The Assessment Group had explained in its assessment report that this trial did not directly report maximum walking distance and had therefore been excluded. However, after consultation the Assessment Group identified data on maximum walking distance from the trial reported in a Cochrane review of naftidrofuryl oxalate for intermittent claudication, noting that it was not possible to validate the data from the original trial. The Assessment Group then undertook a sensitivity analysis to explore the impact on the ICER of including this trial in the meta-analysis. The results indicated that including the trial in the network meta-analysis reduced the estimated effectiveness of naftidrofuryl oxalate. However, naftidrofuryl oxalate continued to have a significant effect and its effectiveness relative to the other vasoactive drugs did not change. Including this data in the economic model increased the ICER for naftidrofuryl oxalate from £6070 (base case) to £8321 per QALY gained.

4.3 Consideration of the evidence

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate having considered evidence on the nature of intermittent claudication in people with peripheral arterial disease and the value placed on the benefits of these drugs by people with the condition, those who represent them, and clinical specialists¹. It also took into account the effective use of NHS resources.
- 4.3.2 The Committee discussed the current clinical management for intermittent claudication in people with peripheral arterial disease. It heard that it is common practice for a specialist vascular clinic to diagnose intermittent claudication before starting drug treatment aimed at relieving symptoms. It also heard that diagnosis and treatment with vasoactive drugs can take place in primary care. The Committee heard from the clinical specialists that vasoactive therapy was an important part of treatment for intermittent claudication, but represents one part of a wider programme of management. This approach involves pharmacological treatment (for example, therapy with antiplatelet drugs and statins to prevent myocardial infarction and stroke) and non-pharmacological treatment including changes in lifestyle (for example, stopping smoking), exercise programmes, and revascularisation (for example, angioplasty). The clinical specialists highlighted the importance of lifestyle changes and exercise programmes, in particular supervised programmes, in the clinical management of the condition, but also that few patients in the NHS had access to supervised programmes in England and Wales. The Committee accepted that that treatment with vasoactive drugs does not

¹ One clinical specialist and a representative of the Guideline Development Group developing the NICE clinical guideline 'Lower limb peripheral arterial disease: diagnosis and management' attended the Appraisal Committee meeting. For the purposes of this document they are both referred to as clinical specialists.

replace or precede the importance of stopping smoking and increasing exercise.

- 4.3.3 The Committee heard from the clinical specialists that vasoactive drugs relieve symptoms but do not delay progression of peripheral arterial disease or lower the incidence of myocardial infarction, stroke or lower extremity amputation. It also heard that most clinicians offer vasodilator therapy only to those patients for whom angioplasty is considered inappropriate or has failed. In addition, the clinical specialists explained that prescribing of vasoactive therapies varies across clinical practice, but that cilostazol and naftidrofuryl oxalate were more commonly prescribed than pentoxifylline and inositol nicotinate. The Committee heard from consultees and commentators that clinicians may offer vasodilator therapy before assessing whether angioplasty would be appropriate, while a patient is awaiting revascularisation, to patients who do not have easy access to a supervised exercise programme or for whom a trial of supervised exercise of 8–16 weeks did not improve the symptoms of claudication. 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 the guideline. For the purposes 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 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 in which vasodilator therapy is deemed the most appropriate treatment option among the other treatment options available, such as exercise therapy or

angioplasty (that is, when the vasodilator drugs would be compared with each other and with best supportive care). The Committee also concluded that drug treatment should not replace referral for consideration of specialist treatment.

4.3.4 The Committee considered groups of patients in which the clinical pathway might differ, and heard from the clinical specialists that patients with diabetes might have atherosclerotic disease that is less likely to respond to angioplasty. The Committee heard that patients with diabetes were more likely to have intermittent claudication than people without diabetes, but that a person with diabetes was more likely than a person without diabetes to have peripheral arterial disease without symptoms of pain. Given the evidence, the Committee accepted that there was no group of patients in which the clinical pathway might differ, and concluded that no specific recommendation for any subgroup of patients would be made.

4.3.5 The Committee discussed the clinical need of people with intermittent claudication. It was aware that severe pain on physical exertion has a large impact on the quality of life, resulting largely from restricted mobility. This may lead to loss of independence, limited social life and decreased participation in recreation and work activities. The Committee concluded that intermittent claudication negatively affects quality of life.

Clinical effectiveness

4.3.6 The Committee considered the evidence for the clinical effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate presented by the Assessment Group. The Committee noted that the trials reported a number of endpoints measuring efficacy including maximum walking distance, pain-free walking distance and ankle brachial pressure index. The Committee heard from the clinical specialists that neither the ankle

brachial pressure index nor pain-free walking distance were clinically relevant outcome measures. The ankle brachial pressure index is used in clinical practice only as a diagnostic tool for peripheral arterial disease, and a patient is unlikely to be offered treadmill testing in the course of routine clinical practice. In addition, pain-free walking distance can be difficult to assess 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.

- 4.3.7 The Committee considered the differences in clinical effectiveness between cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate from the maximum walking distances reported in the randomised controlled trials. It noted that the majority of the trials compared one of the four drugs with placebo and that the only head-to-head comparison was that of cilostazol compared with pentoxifylline. The Committee was aware that the size of the treatment effect reported in the trials for each of the drugs varied. The Committee noted that the publication dates of the included trials span 20 years (from 1989 to 2009) and heard from the Assessment Group that the variation in the size of the treatment effect across these trials was a result of the changes in standard clinical practice over time. The Committee heard from the clinical specialists that a clinically significant improvement in maximum walking distance approximated 50 metres, or, in relative terms, a 100% increase. The Committee also noted that in the trials, patients randomised to either treatment or placebo tended to improve. However, the Committee recognised that the evidence showed that cilostazol and naftidrofuryl oxalate clinically significantly improved maximum walking distance compared with placebo.

4.3.8 The Committee discussed the Assessment Group's network meta-analysis that estimated the change in log maximum walking distance from baseline to the end of the trial. It was aware that the Assessment Group had excluded trials of inositol nicotinate because the trials had follow-up periods of only 12 weeks and it considered the data reported in these trials to be unsuitable for inclusion in the meta-analysis because there was no information reported on proportional change from baseline. The Committee noted from the meta-analysis that treatment with naftidrofuryl oxalate had the greatest effect of the three drugs relative to placebo (that is, a 60% increase from baseline walking distance), followed by cilostazol (25%) and pentoxifylline (11%). Given these results, the Committee considered whether it would be appropriate to infer a difference in the clinical effectiveness of the drugs. The Committee noted the credible intervals around the estimates of effectiveness, which indicated some uncertainty about the true effects. The Committee discussed the duration of follow-up and the heterogeneity between trials. For example, the Committee heard that, in general, the trials did not differentiate between patients who had or had not had previous exercise therapy. The Committee also discussed that only one trial of naftidrofuryl oxalate was included in the meta-analysis. The Committee considered that the above-listed issues contributed to uncertainty in the results of the meta-analysis.

4.3.9 The Committee discussed the duration of follow-up of the trials included in the network meta-analysis. The Committee noted that the trials had a follow-up of 24 weeks, which it understood to be relatively short term compared with clinical practice, in which patients could take vasoactive drugs indefinitely. The Committee heard that trials in which an effect was seen at 24 weeks generally had also showed an effect at 12 weeks. The Committee heard from the clinical specialists that in current clinical practice clinicians stop vasoactive therapy if there is not an adequate response to treatment after 12 weeks. The Committee also heard from the

Assessment Group that the trials of inositol nicotinate excluded from the meta-analysis were excluded for reasons other than their duration (for example, they did not include data on maximum walking distance or were reported in a way that did not allow comparison of results across studies). The Committee heard that there is no agreement about the magnitude of improvement in walking distance needed to define an adequate response to vasoactive therapy. The Committee considered whether the impact of the vasoactive drugs on walking distance was likely to be sustained in the long term. However, the clinical specialists did not expect that if effective treatment was stopped for a reason other than inadequate response that a patient would continue to experience relief of symptoms. The Committee accepted that the duration of follow-up of the trials did not lead to uncertainty around the size of effect.

- 4.3.10 The Committee then considered the differences between the trials included in the network meta-analysis. The Committee considered whether this could lead to bias in the analyses of the comparative clinical effectiveness of cilostazol, naftidrofuryl oxalate and pentoxifylline. The Committee heard from the Assessment Group that the eligibility criteria and baseline characteristics of patients recruited were similar across the trials. 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 exist 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.

4.3.11 The Committee discussed the number of trials of naftidrofuryl oxalate included in the meta-analysis. It noted that only one out of the five trials of naftidrofuryl oxalate compared with placebo identified by the Assessment Group was included in the meta-analysis and in particular that the Assessment Group had excluded the largest trial, which included over 700 participants. The Committee recognised that these trials were excluded because they did not include data on maximum walking distance or that data on maximum walking distance was not comparable across studies. The Committee noted the concerns of some consultees and commentators about the degree of transparency of trial selection. The Assessment Group highlighted that a network meta-analysis is not restricted by the number of the studies for each treatment under evaluation, or by the number of the patients randomised to each treatment arm. The Assessment Group stated that the selection of trials followed a pre-planned protocol that allowed trials to be excluded. 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 (see section 4.1.13). The Committee understood that it was common practice among Assessment Groups to exclude publications in languages other than English because of resource constraints, but agreed that whenever possible non-English language publications should be included to reduce the risk of bias. The Assessment Group informed the Committee that a review of existing trial data was undertaken by the authors of the Cochrane review of naftidrofuryl oxalate for intermittent claudication which suggested that there was no evidence of publication bias. The Committee heard from the Assessment Group that relevant trials that were not published in English may have been missed, but that methodological studies have indicated that language restrictions do not often influence the results of systematic reviews of conventional

medicines. The Committee accepted the Assessment Group's rationale for excluding studies from the meta-analysis and agreed that the Assessment Group's process was transparent.

- 4.3.12 The Committee noted that the Assessment Group had undertaken an additional sensitivity analysis that included data from a trial that it had excluded from its network meta-analysis but that had been highlighted for possible inclusion by the manufacturer (see section 4.2.13). It noted that including this trial 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 cilostazol and pentoxifylline.
- 4.3.13 The Committee noted that the point estimates for maximum walking distance for cilostazol, naftidrofuryl oxalate and pentoxifylline compared with placebo obtained from the meta-analysis were similar to those obtained from the direct estimates from the randomised clinical trials, but were associated with narrower credible intervals, indicating a greater degree of certainty about the effectiveness point estimates. 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. In addition the Committee concluded that naftidrofuryl oxalate had been demonstrated to be more effective than cilostazol and pentoxifylline. Because the meta-analysis did not include any information on the clinical effectiveness of inositol nicotinate, the Committee concluded that it was unable to assess the efficacy of

inositol nicotinate compared with cilostazol, naftidrofuryl oxalate and pentoxifylline.

- 4.3.14 The Committee discussed the 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 acknowledged that the trials were not designed to address mortality, and, in any event, were too short or too small to detect a difference if one existed. The Committee also noted that the clinical specialists 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 the vasodilator drugs being appraised.

Cost effectiveness

- 4.3.15 The Committee examined the economic modelling developed for the appraisal and agreed that the Assessment Group's economic evaluation was of good quality. Because the drugs did not affect the risk of fatal cardiovascular disease, the Committee recognised that the QALYs in the model were driven by the utility gain from increased mobility rather than from any survival benefit. The Committee noted that the utility values used in the model were derived from a regression model using the change in maximum walking distance and SF-36 data, based on patient-level data from a trial of cilostazol compared with placebo. The Committee noted the concerns raised by the manufacturer of cilostazol that there was uncertainty about the association between maximum walking distance and utility because the trial from which the Assessment Group derived the estimates was small ($n = 109$), and the Assessment Group assumed that the association was the same for

all of the vasoactive drugs. 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. It 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 section 6.1).

- 4.3.16 The Committee then considered whether there were any other health-related benefits that had not been adequately captured in the Assessment Group's economic model. It heard from the manufacturer of cilostazol that because of cilostazol's pharmacological profile, the drug improves cardiovascular risk factors (for example, by its anti-platelet actions). The Committee was aware that the CASTLE trial ('Cilostazol: a study in long-term effects'), a randomised, double-blinded, placebo-controlled safety study of cilostazol compared with placebo, was designed to detect a difference in mortality, but found none. The manufacturer informed the Committee that cilostazol was used to prevent strokes, but that this benefit had not been demonstrated in the population identified in this appraisal, that is, people with intermittent claudication. Furthermore, 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 was no evidence available on benefits other than improvement in maximum walking distance related to health-related quality of life.

4.3.17 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 was aware that naftidrofuryl oxalate was associated with the largest QALY gain and the lowest cost, thereby dominating cilostazol and pentoxifylline. The Committee recognised that there was uncertainty associated with the ICERs for naftidrofuryl oxalate because the data for naftidrofuryl oxalate included in the model were originally derived from only one trial. The Committee was aware of the additional sensitivity analysis undertaken by the Assessment Group (see 4.2.13), which indicated that the inclusion of the additional data for naftidrofuryl oxalate within the meta-analysis had a limited impact on the cost-effectiveness results. The Committee agreed that because of the low ICER for naftidrofuryl oxalate, the Committee could accept the uncertainty associated with the ICER. It therefore concluded that it could recommend naftidrofuryl oxalate as a cost-effective use of NHS resources when vasodilator therapy is considered appropriate after taking into account other treatment options, and that treatment with naftidrofuryl oxalate should be started with the least costly licensed preparation. The Committee also agreed that drug treatment should not replace referral for consideration of specialist treatment. The Committee agreed that it could not consider cilostazol and pentoxifylline to be appropriate treatment options, because naftidrofuryl oxalate dominates cilostazol and pentoxifylline. It noted that some consultees and commentators had agreed with the Committee's preliminary decision about this. The Committee noted that the ICERs for cilostazol and pentoxifylline compared with placebo exceeded those normally considered to be an acceptable use of NHS resources. It concluded that cilostazol and pentoxifylline could not be recommended as a cost-effective use of

NHS resources for people with contraindications to naftidrofuryl oxalate.

- 4.3.18 The Committee considered the Assessment Group's threshold analysis of the cost effectiveness of inositol nicotinate. The Committee noted that the estimated QALY gains needed for the ICER of inositol nicotinate compared with placebo to fall below £20,000 or £30,000 per QALY gained were 0.085 or 0.056 respectively. The Committee was aware that these were much higher than the QALY gains actually calculated for naftidrofuryl oxalate (0.015 and 0.010 respectively). The Committee inferred that for inositol nicotinate to be considered cost effective, it would need to demonstrate a considerably greater impact on quality of life from improving maximum walking distance than those demonstrated for the other vasoactive drugs. The Committee did not consider this plausible, because the only trial in the Assessment Group's systematic review that reported that inositol nicotinate did not improve maximum walking distance any more than placebo. The Committee therefore concluded that it could not recommend inositol nicotinate as a cost-effective use of NHS resources.
- 4.3.19 The Committee considered whether its preliminary recommendations were associated with any issues related to equality legislation and the requirement for fairness. The Committee noted that no issues had been highlighted during the scoping exercise or during the course of the appraisal. The Committee was aware that the prevalence of peripheral arterial disease differs between ethnic groups, but concluded that the recommendations do not affect access to the technology for any specific groups.

Summary of Appraisal Committee's key conclusions

TA223	Appraisal title: 'Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease'	Section
Key conclusion		
<p>Naftidrofuryl oxalate is recommended as an option for the treatment of intermittent claudication in people with peripheral arterial disease for whom vasodilator therapy is considered appropriate after taking into account other treatment options. Treatment with naftidrofuryl oxalate should be started with the least costly licensed preparation.</p> <p>Cilostazol, pentoxifylline and inositol nicotinate are not recommended for the treatment of intermittent claudication in people with peripheral arterial disease.</p> <p>Reasons for the recommendations:</p> <ul style="list-style-type: none"> • The Committee concluded that naftidrofuryl oxalate is more effective than cilostazol and pentoxifylline. Because the meta-analysis did not include any trials of inositol nicotinate, the Committee was unable to assess the relative efficacy of inositol nicotinate. • The Committee concluded that there was uncertainty about the ICERs for naftidrofuryl oxalate but that this uncertainty could be accepted in light of the low ICERs of £6070 and £11,060 per QALY gained for the generic and branded preparation of naftidrofuryl oxalate respectively. • Naftidrofuryl oxalate dominated cilostazol and pentoxifylline, and even when compared with placebo the ICERs for cilostazol and pentoxifylline were £50,740 and £54,800 per QALY gained respectively. • From the threshold analysis, the Committee inferred that for inositol nicotinate to be considered cost effective it would need to demonstrate a considerably greater impact on quality of life from improving maximum walking distance than those demonstrated for the other vasoactive drugs. The Committee did not consider this assumption plausible, because the only trial in the Assessment Group's systematic review that reported maximum walking distance for inositol nicotinate did not show an improvement in maximum walking distance any greater than for placebo. 		<p>4.3.13</p> <p>4.3.17</p> <p>4.3.17</p> <p>4.3.18</p>
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee was aware that severe pain on physical exertion has a large impact on the quality of life, resulting largely from restricted mobility. This may lead to loss of independence, limited social life and decreased participation in recreation and work activities. The Committee concluded that intermittent claudication negatively affects quality of life.	4.3.5

The technology		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate are vasodilator drugs and have marketing authorisations for the symptomatic relief of intermittent claudication.</p> <p>No specific claims of innovation were made.</p>	2.7
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee heard from the clinical specialists that vasoactive therapy was an important part of treatment for intermittent claudication, but represents one part of a wider programme of management. This approach involves pharmacological (for example, therapy with antiplatelet drugs and statins to prevent myocardial infarction and stroke) and non-pharmacological treatment including changes in lifestyle (for example, stopping smoking), exercise programmes, and revascularisation (for example, angioplasty). The Committee accepted that treatment with vasoactive drugs does not replace or precede the importance of stopping smoking and increasing exercise.</p> <p>The Committee heard from consultees and commentators that clinicians may offer vasodilator therapy before assessing whether angioplasty would be appropriate, while a patient is waiting revascularisation, to patients who do not have easy access to a supervised exercise programme or for whom a trial of supervised exercise of 8–16 weeks did not improve the symptoms of claudication. 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 the guideline.</p>	<p>4.3.2</p> <p>4.3.3</p>
<p>Adverse effects</p>	<p>The Committee 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 concluded that, based on the currently available information, there were no major concerns about the adverse effects of the vasodilator drugs being appraised.</p>	4.3.14

Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The trials reported a number of endpoints measuring efficacy including maximum walking distance, pain-free walking distance and ankle brachial pressure index. The Committee agreed that it was appropriate to focus on the Assessment Group's analyses of maximum walking distance.	4.3.6
	The majority of the trials compared the four drugs with placebo and that one trial compared cilostazol with pentoxifylline.	4.3.7
	The Assessment Group undertook a network meta-analysis that estimated the change from baseline in log maximum walking distance. The network meta-analysis excluded trials of inositol nicotinate.	4.3.8
Relevance to general clinical practice in the NHS	No specific issues were raised.	
Uncertainties generated by the evidence	The Committee noted the credible intervals (from the network meta-analysis of maximum walking distance) around the estimates of effectiveness, which indicated some uncertainty about the true effects. The Committee discussed the duration of follow-up and the heterogeneity between trials. The Committee considered that the above-listed issues contributed to uncertainty in the results of the meta-analysis.	4.3.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee considered groups of patients in which the clinical pathway might differ, and heard from the clinical specialists that patients with diabetes might have atherosclerotic disease that is less likely to respond to angioplasty. The Committee accepted that there was no group of patients in which the clinical pathway might differ and concluded that no specific recommendation for any subgroup would be made.	4.3.4

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>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.</p> <p>The Committee noted from the meta-analysis that treatment with naftidrofuryl oxalate had the greatest effect relative to placebo (that is, a 60% increase from baseline walking distance), followed by cilostazol (25%) and pentoxifylline (11%). The Committee noted the credible intervals around the estimates of effectiveness, which indicated that there was some uncertainty about the true effects. The Committee considered the duration of follow-up and the heterogeneity between trials and the inclusion of only a single trial of naftidrofuryl oxalate, because these contributed to the uncertainty in the results of the meta-analysis. The Committee concluded that the Assessment Group may have over-estimated the clinical effectiveness of naftidrofuryl oxalate as a result of excluding trials but was persuaded by the evidence presented that naftidrofuryl oxalate had the largest effect compared with cilostazol and pentoxifylline.</p> <p>Because the meta-analysis did not include any information on the clinical effectiveness of inositol nicotinate, the Committee concluded that it was unable to assess the efficacy of inositol nicotinate compared with cilostazol, naftidrofuryl oxalate and pentoxifylline.</p>	<p>4.3.7</p> <p>4.3.8-4.3.12</p> <p>4.3.13</p>
Evidence for cost effectiveness		
<p>Availability and nature of evidence</p>	<p>None of the manufacturers submitted economic evaluations or economic models.</p> <p>The Committee agreed that the Assessment Group's economic evaluation was of good quality.</p>	<p>4.3.15</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee noted that the utility values used in the model were derived from a regression model using the change in maximum walking distance and SF-36 data, based on patient-level data from a trial of cilostazol compared with placebo. The Committee noted the concerns raised by the manufacturer of cilostazol that there was uncertainty about the association between maximum walking distance and utility because the trial from which the estimate was derived was small and the Assessment Group had assumed that the association was the same for all vasoactive drugs. However, the Committee noted that the order of the utility values was consistent with the order of effectiveness of the vasoactive</p>	<p>4.3.15</p>

	<p>drugs as shown in the meta-analysis. The Committee 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.</p>	
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>Because the drugs did not affect the risk of fatal cardiovascular disease, the Committee recognised that the QALYs in the model were driven by the utility gain from increased mobility rather than from any survival benefit.</p> <p>The Committee considered whether there were any other health-related benefits that had not been adequately captured in the Assessment Group's economic model. It heard from the manufacturer of cilostazol that because of cilostazol's pharmacological profile, the drug improves cardiovascular risk factors. The manufacturer informed the Committee that cilostazol was used to prevent strokes, but that this benefit had not been demonstrated in the population defined in this appraisal. Furthermore, the Committee noted that the manufacturer had not submitted any evidence related to these potential benefits. 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 was no evidence available on benefits other than improvement in maximum walking distance related to health-related quality of life.</p>	<p>4.3.15</p> <p>4.3.16</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>Not applicable.</p>	
<p>What are the key drivers of cost effectiveness?</p>	<p>No key drivers were identified apart from the differences between treatment costs and utility values related to the differences in maximum walking distance.</p>	
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee recognised that there was uncertainty associated with the ICERs for naftidrofuryl oxalate compared with placebo (£11,060 for the branded version, £6070 for the generic version) because the data for naftidrofuryl oxalate included in the model were originally derived from only one trial. The Committee was aware of the additional sensitivity analyses undertaken by the Assessment Group, which</p>	<p>4.2.13, 4.3.17</p>

	<p>indicated that the inclusion of the additional data for naftidrofuryl oxalate within the meta-analysis had a limited impact on the cost-effectiveness results (£8321 per QALY gained). The Committee agreed that because of the low ICERs for naftidrofuryl oxalate, it could accept the uncertainty associated with the ICERs.</p> <p>The Committee noted that naftidrofuryl oxalate was associated with the largest QALY gain and lowest cost, thereby dominating cilostazol and pentoxifylline. The Committee also noted that the ICERs for cilostazol and pentoxifylline were £50,700 and £54,800 per QALY gained respectively when each was compared with placebo.</p> <p>The Committee inferred that for inositol nicotinate to be considered cost effective, it would need to demonstrate considerably greater impacts on quality of life from improving maximum walking distance than those demonstrated for the other vasoactive drugs. The Committee did not consider this assumption plausible, because the only trial in the Assessment Group's systematic review that reported maximum walking distance for inositol nicotinate did not show an improvement in maximum walking distance any greater than for placebo.</p>	4.3.18
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	The Committee noted that no issues had been highlighted during the scoping exercise or during the course of the appraisal. The Committee was aware that the prevalence of peripheral arterial disease differs between ethnic groups, but concluded that the recommendations do not affect access to the technology for any specific groups.	4.3.19

5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TA223).
- Costing template and report to estimate the national and local savings and costs associated with implementation.
 - Audit support for monitoring local practice.

6 Recommendations for further research

- 6.1 A trial comparing the long-term effectiveness (beyond 24 weeks) of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate and placebo would be beneficial. It should collect utility data as well as walking distance outcomes.

7 Related NICE guidance

Published

- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of NICE technology appraisal guidance 90). NICE technology appraisal guidance 210 (2010). Available from www.nice.org.uk/guidance/TA210

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Lower limb peripheral arterial disease. NICE clinical guideline. Publication expected October 2012.

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review in May 2014. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon

Chief Executive

May 2011

Appendix A: Appraisal Committee members, guideline representative and NICE project team

A *Appraisal Committee members*

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between the Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital, Cambridge

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Dr Michael Boscoe

Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust, London

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty

External Relations Director – Pharmaceuticals & Personal Health, Oral Care Europe

Mrs Eleanor Grey

Lay member

Mr Sanjay Gupta

YPD Service Case Manager, Southwark Health and Social Care, Southwark PCT

Dr Neil Iosson

GP, Brighton and Chichester

Mr Terence Lewis

Lay member

Dr Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Rubin Minhas

GP, Medway, Kent; Clinical Director, BMJ Evidence Centre

Dr Peter Norrie

Principal Lecturer in Nursing, DeMontfort University

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel

Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital, Surrey

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Casey Quinn

Lecturer in Health Economics, Division of Primary Care, University of Nottingham

Mr Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Dr Florian Alexander Ruths

Consultant Psychiatrist and Cognitive Therapist, Maudsley Hospital, London

Mr Navin Sewak

Primary Care Pharmacist, NHS Hammersmith and Fulham, London

Mr Roderick Smith

Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling

Lay member

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor

Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

Mr Tom Wilson

Director of Contracting & Performance, NHS Tameside & Glossop

B ***Guideline representative***

The following individual, representing the Guideline Development Group responsible for developing NICE's clinical guideline related to this topic, was invited to attend the meeting to observe and to contribute as an adviser to the Committee:

- Professor Jonathan Michaels, Professor of Vascular Surgery, University of Sheffield

C ***NICE project team***

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Panagiota Vrouchou

Technical Lead

Nicola Hay

Technical Adviser

Jeremy Powell

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by the School of Health & Related Research Sheffield:

- Squires H, Simpson E, Meng Y et al. Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease, October 2010

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Otsuka

II Professional/specialist and patient/carer groups:

- British Cardiovascular Intervention Society (BCIS)
- British Heart Foundation
- Royal College of Nursing
- Royal College of Physicians

III Other consultees:

- Department of Health
- NHS Luton
- NHS Salford
- Welsh Assembly Government

IV Commentator organisations (without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency
- NHS Quality Improvement Scotland

C The following individual was selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Mr Constantinos Kyriakides, Consultant Vascular Surgeon, Barts and The London NHS Trust, nominated by Otsuka Pharmaceuticals – clinical specialist

D Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Otsuka