NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

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

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

1 Background

1.1 The condition

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, which is narrowing of the arteries caused by fatty deposits on the arterial walls.

The Fontaine classification scheme includes four different stages of PAD. PAD can be asymptomatic (Fontaine classification I) or symptomatic (Fontaine classification II–IV). The most common symptom of PAD is intermittent claudication (Fontaine classification II), which is characterised by pain in the legs or buttocks that occurs with exercise and is relieved with rest. People with severe pain at rest (ischaemic rest pain, Fontaine classification III) can progress to necrosis and gangrene (Fontaine classification IV).

The pain that people experience with intermittent claudication is a result of the narrowed arteries not delivering adequate blood to leg muscles and so pain comes from the oxygen starved muscles. Pain is relieved with rest because of normalisation of the blood flow. Intermittent claudication is most commonly

associated with PAD in the femoropopliteal segment. PAD can also be present at the aorto-iliac level causing pain in the thigh, hip or buttock. In rare cases PAD can be located in the foot.

The major risk factors of intermittent claudication are smoking and diabetes mellitus. Other factors include hypertension, hypercholesterolaemia, obesity, renal insufficiency, hyperhomocysteinaemia, raised C-reactive protein and sedentary lifestyle. People 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 patients with PAD who do not have intermittent claudication.

The prevalence of intermittent claudication increases with age and is more common in men than women. Intermittent claudication has a detrimental effect on people's quality of life because of their restricted mobility. Around 20% of people aged 55–75 years have evidence of PAD in the legs and a quarter of them have symptoms.

The diagnosis of intermittent claudication includes an assessment of the presence or absence and type of pain that a patient experiences. A measurement of patient's ankle-brachial pressure index (ABPI) at rest is also taken.

1.2 Current management

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 the recommendation to exercise. Supervised exercise programmes are the most effective form of exercise but are not widely available in England and Wales. Additionally, antiplatelet drugs and statins might be offered as long-term prophylaxis of myocardial infarction and stroke. Vasoactive drugs (that is

cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate) are offered for the relief of intermittent claudication symptoms only as their use do not have an impact on the progression of the disease.

Clinical practice for people whose symptoms continue despite a period of conventional management varies. Clinicians might consider whether angioplasty is appropriate and if so undertake it immediately. If angioplasty is either not appropriate or fails, people might receive vasoactive treatment. Alternatively, people might be offered vasoactive treatment independent of whether or not they may be considered for angioplasty. If vasoactive treatment is not successful then these people might be considered for angioplasty, if considered appropriate. If vasoactive treatment is successful, then it might negate or delay the need for angioplasty.

NICE guidance

Published

Clopidogrel and modified-release dipyridamole in 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

Diagnosis and management of lower limb peripheral arterial disease in adults. NICE clinical guideline (publication expected October 2012).

Other guidance

Diagnosis and management of peripheral arterial disease. SIGN clinical guideline 89 (2006). Available from www.sign.ac.uk/guidelines/fulltext/89/index.html

2 The technologies

Summary description of technologies

Generic name	Cilostazol	Naftidrofuryl oxalate	Pentoxifylline	Inositol nicotinate
Brand name	Pletal	Praxilene	Trental 400	Hepoxal
Brand manufacturer	Otsuka Pharmaceuticals	Merk Serono	Sanofi-Aventis	Genus Pharmaceuticals
Generic manufacturer	–	Actavis UK. Kent Pharmaceuticals. Mylan Teva.	Apotex UK	Mylan
Dose	200 mg daily (100 mg twice daily).	300 mg or 600 mg daily (one or two 100 mg capsules three times daily).	Recommended initial dose: 1200 mg daily (one tablet of 400 mg three times daily); 800 mg daily dose (two 400 mg tablets daily) may prove sufficient in some patients.	3 g daily (2 to 3 divided doses daily). Dose might be increased to 4 g daily if necessary.
Acquisition cost (British national formulary 60)	£35.31 (100 mg, 56-tablet pack)	Merk Serono £8.10 (net price 84-capsule pack) £5.30 (net price 84-capsule pack)	£19.68 (400 mg, net price 90-tablet pack)	£30.76 (500 mg, net price 100-tablet pack) £51.03 (750 mg, net price 112-tablet pack).

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 (that is, for peripheral arterial disease Fontaine stage II). 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, pregnancy. Cilostazol is also contraindicated in patients with any known

predisposition to bleeding and with any history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics. For full details of side effects and contraindications see the summary of product characteristics.

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. 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.

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. 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.

Inositol nicotinate (Hepoxal, 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. Inositol nicotinate is contraindicated in people who have suffered a recent myocardial infarction or are in the acute phase of a cerebrovascular accident. It also contraindicated in patients hypersensitive to the active ingredient. For full details of side effects and contraindications see the summary of product characteristics.

According to evidence from the Prescription costs analysis, England (2009) the market share of cilostazol is 29%, naftidrofuryl is 52%, pentoxifylline is 4% and inositol nicotinate is 15% in England and Wales.

3 The evidence

3.1 Clinical evidence

3.1.1 Manufacturer's submission

Only one manufacturer (Otsuka) submitted clinical evidence on the treatment of intermittent claudication in people with peripheral arterial disease. The submission included 11 randomised control trials (RCTs) that assessed the efficacy and/or safety of cilostazol. Ten of the RCTs assessed the efficacy of cilostazol compared with placebo. Three of these studiers also compared cilostazol with pentoxifylline. The eleventh study (CASTLE) was primarily designed to assess safety. The submission also included a meta-analysis (Pande et al, 2010) of the results of 9 of the trials comparing cilostazol with placebo or pentoxifylline. The submission did not present clinical evidence on cilostazol compared with naftidrofuryl oxalate and inositol nicotinate.

Compared with placebo, cilostazol improved maximal walking distance, and statistical significance was achieved in seven out of ten trials. Results for pain free walking distance also demonstrated an improvement with cilostazol when compared with placebo. Statistical significance was achieved in five out of the ten trials. The results of the meta-analysis confirmed the findings of the individual trials. In addition the meta-analysis reported that pentoxifylline did not show a significant improvement in the absolute distance claudication when compared with placebo.

All of the studies included in the submission were also indentified and included in the Assessment Group's systematic review.

3.1.2 Assessment Group report

Systematic review of existing clinical effectiveness evidence

The Assessment Group identified four Cochrane reviews; three reviews of cilostazol (Pratt, 2001; Robless et al, 2008; Pande et al, 2010) and one review of naftidrofuryl oxalate (De-Backer-Tine et al, 2008). All of the trials included in the three reviews of cilostazol were included in the systematic review undertaken by the Assessment Group. Only three out of the six trials included in the review of naftidrofury oxalate were included in the systematic review undertaken by the Assessment Group because the naftidrofuryl oxalate dose was not in line with the UK marketing authorisation, or the population included patients with severe pain at rest (ischemic rest pain).

Assessment Group's systematic literature review

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 PAD whose symptoms continue despite a period of conventional management.

A total of 26 RCTs in 36 publications were indentified. Placebo-controlled trials were available for all four of the vasoactive drugs being assessed in the appraisal. The only head-to head comparison between the vasoactive drugs was that of cilostazol versus pentoxifylline. The included studies provided data for the following comparisons:

- 11 RCTs of cilostazol 200 mg versus placebo
- three RCTs of cilostazol 200 mg versus pentoxifylline 1200 mg
- one RCT of cilostazol 200 mg (with or without supervised exercise) versus usual care (with or without supervised exercise)
- four RCTs of naftidrofuryl oxalate 600 mg versus placebo
- one RCT of naftidrofuryl oxalate 300 mg versus placebo
- nine RCTs of pentoxifylline 1200 mg versus placebo
- three RCTs of inositol nicotinate 4 g versus placebo.

Three of the trials (comparing cilostazol with placebo or pentoxifylline) have not been published (to date) as trial reports The Assessment Group obtained information about these trials from the three Cochrane reviews of cilostazol and from the manufacturer's submission. Additional information on the naftidrofuryl oxalate trials was obtained from the Cochrane review of naftidrofuryl oxalate.

Cilostazol

Eleven RCTs in 11 publications (n = 1435, n = 106, n = 262, n = 466, n = 345, n = 247, n = 520, n = 239, n = 81, n = 189, n = 142) comparing cilostazol with placebo or pentoxifylline met the inclusion criteria for the Assessment's systematic review. Eight RCTs compared cilostazol (200 mg) with placebo and three compared cilostazol with pentoxifylline (1200 mg) and placebo. The treatment duration of the RCTs ranged from 12 weeks to 24 weeks; 6 had a treatment duration of 24 weeks, one of 16 weeks and 3 of 12 weeks. The outcomes included in these trials were maximum walking distance, pain-free walking distance, ABPI, cardiovascular events, mortality, adverse events and health related quality of life. The baseline age of the participants receiving cilostazol ranged from 63-67 years of age. Only one out of the eleven RCTs recruited patients from the UK (n = 106). For further details of these trials see pages 141–180 of the assessment report.

One RCT in one publication (n = 34) met the inclusion criteria for this review. In this RCT (Hobbs et al 2007) cilostazol 200 mg (with or without supervised exercise) was compared with usual care (with or without supervised exercise). The treatment duration was 24 weeks, the outcomes included were maximum and pain-free walking distance. The baseline age of the participants receiving cilostazol was 58 years of age. The trial recruited 38 patients from the UK. For further details of this trial see pages 229 –231 of the assessment report.

Naftidrofuryl oxalate

Five RCTs in five publications (n = 74, n = 196, n = 118, n = 104, n = 50) met the inclusion criteria for the Assessment's Group review. Four RCTs compared naftidrofuryl oxalate 600 mg with placebo and one compared

naftidrofuryl oxalate 300 mg with placebo. The treatment duration of the trials ranged from 12 weeks to 24 weeks; three had a treatment duration of 24 weeks and two had a treatment duration of 12 weeks. The outcomes included in these studies were maximum walking distance, pain-free walking distance, ABPI, cardiovascular events, mortality, adverse events and health related quality of life. The baseline age of the participants receiving naftidrofuryl oxalate in three of the trials ranged from 58-67 years of age. Baseline age of participants in the remaining trials was not reported in the assessment report. Only one RCT recruited UK patients (n = 50). For further details of these trials see pages 181–195 of the assessment report.

Pentoxifylline

Nine RCTs in nine publications (n = 74, n = 170, n = 471, n = 150, n = 128, n = 247, n = 524, n = 48, n = 24) met the inclusion criteria for the Assessment Group review. Six RCTs compared pentoxifylline 1200 mg with placebo and three compared pentoxifylline 1200 mg with cilostazol and placebo. The treatment duration of the RCTs 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, ABPI, cardiovascular events (and cardiovascular events leading to withdrawal), mortality, adverse events and health related quality of life. The baseline age of the participants receiving pentoxifylline ranged from 59-68 years of age. None of the nine RCTs recruited patients from the UK. For further details of these trials see pages 169–180 and 196–218 of the assessment report.

Inositol nicotinate

Three RCTs in three publications (n = 120, n = 80, n = 123) met the inclusion criteria for the Assessment's Group review. All RCTs compared inositol nicotinate 4 g with placebo and had treatment duration of 12 weeks. The outcomes included in these studies were pain-free walking paces, maximum walking distance, ABPI, time to claudication, cardiovascular events leading to withdrawal, mortality and adverse events leading to withdrawal. The baseline

age of the participants receiving inositol nicotinate ranged from 61-68 years of age. All RCTs recruited UK patients (n = 120, n = 80, n = 123). For further details of these trials see pages 219–228 of the assessment report.

Quality assessment

The Assessment Group considered the quality of the trials to be generally good: treatment groups within trials were comparable, blinding was maintained and trials presented intention-to-treat analyses. For further details of the Assessment Group's quality assessment of the trials see pages 36–38 of the assessment report.

The Assessment Group stated that the results of these trials are generalisable across all patients in the UK who have stable (at least for the past 3 months) and symptomatic intermittent claudication, secondary to peripheral arterial disease, whose symptoms continue despite a period of conventional management. However, there might be a subgroup of people with more severe intermittent claudication in which treatment with vasoactive drugs might prevent the need for angioplasty.

A brief summary of the results of the systematic review is given below. The Assessment Group provided a narrative synthesis of the treatment effect for all outcomes and a network meta-analysis was also undertaken for mean walking distance and pain free walking distance.

Results of the clinical effectiveness review

Maximum walking distance is a measure of how far a person can walk before symptoms of intermittent claudication prevent them from walking. Pain-free walking distance is a measure of the distance walked before a person starts experiencing pain due to intermittent claudication. The European Medicines Agency (EMA) recommends that treadmill tests should be performed to assess claudication distances. The EMA specifies two internationally recognised treadmill protocols; constant workload treadmill protocol and the graded test treadmill protocol. The constant workload treadmill protocol involves setting the treadmill a fixed slope at a fixed speed. The graded

treadmill protocol involves setting the treadmill at a fixed speed with the slope increased by a pre-set amount at regular intervals.

Maximum walking distance

Ten of the eleven trials of cilostazol 200 mg compared with placebo reported this outcome. Seven out of the ten trials showed a statistically significant improvement in maximum walking distance for the cilostazol group compared with the placebo group. Table 1 presents results from published trial reports for cilostazol compared with placebo.

Table 1 Cilostazol 200 mg versus placebo (maximum walking distance)

Trial	Number of participants	Treadmill protocol	Results – change in maximum walking distance
O'Donnell et al 2009 (24 weeks)	Cilostazol = 51. Placebo = 55.	Constant	Cilostazol = 161.7% mean improvement. Placebo = 79% mean improvement. p = 0.048.
Strandness et al 2002 (24 weeks)	Cilostazol = 133. Placebo = 129.	Constant	Cilostazol = 76.2 m mean improvement. Placebo = 21.1 m mean improvement. p = 0.0003.
Dawson et al 2000 (24 weeks)	Cilostazol = 227. Placebo = 239.	Graded	Cilostazol = 107 m (SD 158 m) mean improvement. Placebo = 65 m (SD 135 m) improvement. p = 0.0005.
Beebe et al 1999 (24 weeks)	Cilostazol = 175. Placebo = 170.	Constant	Cilostazol = 129.1 m mean improvement. Placebo = 26.8 m mean improvement. p < 0.001.
Money et al 1998 (16 weeks)	Cilostazol = 119. Placebo = 120.	Graded	Cilostazol = 96.4 m mean improvement. Placebo = 31.4 m mean improvement. p < 0.05.
Dawson et al 1998 (12 weeks)	Cilostazol = 54. Placebo = 27.	Constant	Cilostazol = 30.5% improvement. Placebo = −9.3% change (worsening). p < 0.01.
Elam et al 1998 (12 weeks)	Cilostazol = 95. Placebo = 94.	Graded	Cilostazol = 72.7 m mean improvement. Placebo = 25.8 m mean improvement. p = 0.004.
SD = standard deviation.			

The Assessment Group stated that using different treadmill protocols might explain the heterogeneity observed in the trials. The three trials that reported a graded treadmill protocol reported a statistically significant improvement in maximum walking distance in the cilostazol groups compared with placebo.

However, of the seven trials using the constant workload protocol, four reported that cilostazol statistically significantly improved maximum walking distance compared with placebo while three did not. The Assessment Group stated that the length of follow-up and the sample size cannot explain the differences between the significance and non-significance of the results reported in the trials that used the constant workload protocol.

All three trials that compared cilostazol with pentoxifylline reported the outcome of maximum walking distance. Only one trial found a statistically significant improvement in maximum walking distance for cilostazol compared with pentoxifylline (p = 0.0002). The other two studies showed no significant difference between cilostazol and pentoxifylline. Table 2 presents the results from published trial reports for cilostazol compared with pentoxifylline.

Table 2 Cilostazol 200 mg versus pentoxifylline 1200 mg (maximum walking distance)

Trial	Number of participants	Treadmill protocol	Results – change in maximum walking distance
Dawson et al et al2000 (24 weeks)	Cilostazol = 227. Pentoxifylline = 232.	Graded	Cilostazol = 107 m (SD 158 m) mean improvement. Pentoxifylline =64 m (SD 127 m) mean improvement. p = 0.0002.
SD = standard deviation.			

One trial by Hobbs et al (2007; table 3) compared cilostazol (with or without supervised exercise) with usual care (with or without supervised exercise). The results of this trial showed that all treatment groups were improved but there was a more significant improvement when cilostazol was added to supervised exercise of usual care (p = 0.005).

Table 3 Cilostazol 200 mg versus usual care with or without supervised exercise (maximum walking distance)

Trial	Number of participants	Treadmill protocol	Results – change in maximum walking distance
Hobbs et al 2007 (24 weeks)	Cilostazol = 16 (7 with exercise, 9 without exercise) Usual care = 18 (9 with exercise, 9 without exercise.	Constant	Cilostazol mean ratio with exercise = 2.58 (SD 1.39) improvement. Cilostazol mean ratio without exercise = 1.69 (SD 0.59) improvement. Usual care mean ratio with exercise = 1.45 (SD 0.80) improvement. Usual care mean ratio without exercise = 1.09 (SD 0.34) improvement. Difference in effect = 1.64; p = 0.005.
SD = standard deviation.			

Two trials of naftidrofuryl oxalate 600 mg compared with placebo (table 4) 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 ($p< 0.001$).

Table 4 Naftidrofuryl 600 mg versus placebo (maximum walking distance)

Trial	Number of participants	Treadmill protocol	Results – change in maximum walking distance
Kieffer et al 2001 (24 weeks)	Naftidrofuryl = 98 Placebo = 98	Constant	Naftidrofuryl = 158.7 m mean improvement Placebo = 28.1 m mean improvement p<0.001
Trubestein et al 1984 (12 weeks)	Naftidrofuryl = 54 Placebo = 50	Constant	Naftidrofuryl = 122 m mean improvement Placebo = 90 m mean improvement p = not significant

The Assessment Group stated that this difference might be due to the different length of follow-up; 24 weeks in one study and 12 weeks in the other. Both trials employed the same workload treadmill protocol, had similar study designs and there was very little difference between the two trials in baseline maximum walking distance.

Eight trials of pentoxifylline 1200 mg reported the outcome of maximum walking distance. Two of the eight trials showed a statistically significant improvement in maximum walking distance for the pentoxifylline group compared with placebo. Table 5 presents the results from published trial reports for pentoxifylline compared with placebo.

Table 5 Pentoxifylline 1200 mg versus placebo (maximum walking distance)

Trial	Number of participants	Treadmill protocol	Results – change in maximum walking distance
Creager et al 2008 (24 weeks)	Pentoxifylline = 86. Placebo = 84.	Graded	Pentoxifylline = 13.90% improvement. Placebo = 3.30% improvement. p = 0.039.
Dawson et al 2000 (24 weeks)	Pentoxifylline = 232 Placebo = 239	Graded	Pentoxifylline = 64 m mean improvement. Placebo = 65 m mean improvement. p = 0.82.
Lindgarde et al 1989 (24 weeks)	Pentoxifylline = 76 Placebo = 74	Constant	Pentoxifylline = geometric mean 50% improvement (SE 9). Placebo = geometric mean 29% improvement (SE 8). p = 0.094.
Porter and Bauer1982 (24 weeks)	Pentoxifylline = 67 Placebo = 61	Constant	Pentoxifylline = geometric mean 33% improvement (SE 8). Placebo = geometric mean 20% improvement (SE 7). 2-sided p = 0.316; 1-sided p = 0.049.
Gallus et al 1985 (8 weeks)	Pentoxifylline = 25 Placebo = 23	Constant	Pentoxifylline = geometric mean 23% improvement Placebo = geometric mean 17% improvement Ratio of percentage change from baseline (pentoxifylline/placebo) 1.05 (95% CI 0.81 to 1.36) p = not significant
Di Perri and Guerini 1983 (8 weeks)	Pentoxifylline = 12 Placebo = 12	No treadmill – horizontal ground	Pentoxifylline = 136 m mean improvement Placebo = 6 m mean improvement p < 0.01
SE = standard error.			

Only one of the three trials comparing inositol nicotinate 4 g with placebo (table 6) reported the outcome of maximum walking distance. The results of this trial showed no statistically significant difference between the two groups.

Table 6 Inositol nicotinate 4 g versus placebo (maximum walking distance)

Trial	Number of participants	Treadmill protocol	Results – change in maximum walking distance
Kiff and Quick 1998 (12 weeks)	Inositol nicotinate = 40 Placebo = 40	Patient walked at own pace on a constant slope	Inositol nicotinate = 65.4 m mean improvement. Placebo = 102.8 m mean improvement. p = not significant.

Maximum walking distance meta-analysis

The Assessment Group conducted two meta-analyses of the data for maximum walking distance. The Assessment Group undertook a re-analysis in terms of change from baseline in absolute walking distance of the seven trials that compared cilostazol with placebo that were included in both the Assessment Group's systematic review and the Cochrane review undertaken by Robless et al. (2008). The random effects meta-analysis of the change from baseline in absolute walking distance showed that the treatment with cilostazol compared with placebo resulted in an increase of 52.27 metres (95% credible interval 24.93 to 86.57). Further details of the meta-analysis can be found on pages 44–5 of the Assessment report.

The Assessment Group also undertook a network meta-analysis of the data for maximum walking distance for the overall comparison of treatment options. This consisted of an analysis of the change from baseline in log mean walking distance (log metre) from ten out of the twenty six trials (leading to 16 comparisons) that the Assessment Group had indentified for cilostazol, naftidrofuryl oxalate and pentoxifylline. The Assessment Group stated that inositol nicotinate was not included in the meta-analysis because of the lack of 24-week data. The rationale for the exclusion of the remaining trials is provided in table 20 on page 46 of the assessment report. The network of evidence consisted of seven 2-arm, and three 3-arm, 24 week trials. The network of evidence is shown in figure 2 on page 47 of the assessment report.

The Assessment Group stated that the rationale for transforming the data to the logarithm scale was to produce a scale on which the treatment effects could be assumed to be linear.

The random effects meta-analysis of the change from baseline in log walking distance showed that treatment with naftidrofuryl had the greatest increase (60.3%) compared with placebo, followed by cilostazol (24.6%) and pentoxifylline (10.6%). The 95% credible intervals for naftidrofuryl oxalate and cilostazol compared with placebo showed that there was a real increase in the percentage change from baseline walking distance, although there was some uncertainty as to the true effect. For further details on the 95% credible intervals see table 23 on page 49 of the assessment report. The Assessment Group stated that variation between studies was moderate, suggesting that the treatment effect varied depending on the characteristics of the study. For further information on the meta-analysis see pages 48–51 of the assessment report.

Pain free walking distance

Ten trials of cilostazol 200 mg reported this outcome. Five trials showed a statistically significant improvement in pain-free walking distance for the cilostazol group compared with the placebo group. Table 7 presents results from published trial reports for cilostazol compared with placebo.

Table 7 Cilostazol 200 mg versus placebo (pain free walking distance)

Trial	Number of participants	Treadmill protocol	Results – change in pain-free walking distance
O'Donnell et al 2009 (24 weeks)	Cilostazol = 51. Placebo = 55.	Constant	Cilostazol = 67% improvement. Placebo = 51.6% improvement. p = 0.63.
Strandness et al 2002 (24 weeks)	Cilostazol = 133. Placebo = 129.	Constant	22% (favours cilostazol).
Dawson et al 2000 (24 weeks)	Cilostazol = 227. Placebo = 239.	Graded	Cilostazol = 94 m (SD 127) mean. Placebo = 57 m (SD 93) mean. p = 0.0001.
Beebe et al 1999 (24 weeks)	Cilostazol = 175. Placebo = 170.	Constant	Cilostazol = 67.5 m (59%) mean improvement. Placebo = 23.1 m (20%) mean improvement. p < 0.001.
Money et al 1998 (16 weeks)	Cilostazol = 119. Placebo = 120.	Graded	p < 0.05.
Dawson et al 1998 (12 weeks)	Cilostazol = 54. Placebo = 27.	Constant	Cilostazol = 31.7% improvement. Placebo = −2.5% change (worsening). p<0.01.
SD = standard deviation			

Of the trials that used the constant treadmill protocol, three out of seven showed that cilostazol statistically significantly improved pain-free walking distance compared with placebo. The Assessment Group stated that the length of follow-up and the sample size cannot explain the differences between the significance and non-significance of the results reported in the trials that used the constant workload protocol. In the trials using the graded treadmill protocol, two out of three trials showed a statistically significant improvement in the pain-free walking distance outcome in the cilostazol group compared with the placebo group.

Three trials of cilostazol compared with pentoxifylline reported the outcome of pain-free walking distance. Only one trial found a statistically significant improvement in pain-free walking distance for the cilostazol group compared with the pentoxifylline group. Table 8 presents results from published trial reports for cilostazol compared with pentoxifylline.

Table 8 Cilostazol 200 mg versus pentoxifylline 1200 mg (pain-free walking distance)

Trial	Number of participants	Treadmill protocol	Results – change in pain-free walking distance
Dawson et al 2000 (24 weeks)	Cilostazol = 227 Pentoxifylline = 232	Graded	Cilostazol = 94 m (SD 127) mean. Pentoxifylline = 74 m (SD 106) mean. 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 treatment groups, but there was no significant effect of cilostazol when added to supervised exercise of usual care (table 9).

Table 9 Cilostazol 200 mg versus usual care with or without supervised exercise (pain-free walking distance)

Trial	Number of participants	Treadmill protocol	Results –change in pain-free walking distance
Hobbs et al 2007 (24 weeks)	Cilostazol = 16 (7 with exercise, 9 without). Usual care = 18 (9 with exercise, 9 without).	Constant	Cilostazol with exercise mean ratio = 3.84 (SD 3.62). Cilostazol without exercise mean ratio = 3.34 (SD 4.23). Usual care with exercise mean ratio = 2.22 (SD 2.71). Usual care without exercise mean ratio = 1.23 (SD 0.73). Difference in effect = 2.07; p = 0.090.
SD = standard deviation			

Five trials that compared 600 mg of naftidrofuryl oxalate with placebo reported the outcome of pain-free walking distance. Four of the trials showed a statistically significant improvement in pain-free walking distance for the naftidrofuryl oxalate group compared with the placebo group. Table 10 presents results from published trial reports for naftidrofuryl oxalate compared with placebo.

Table 10 Naftidrofuryl 600 mg versus placebo (pain-free walking distance)

Trial	Number of participants	Treadmill protocol	Results –change in pain-free walking distance
Spengel et al 2002 (24 weeks)	Naftidrofuryl = 382. Placebo = 372.	Not treadmill – patient estimate only	Naftidrofuryl = 204 m (SD 433) mean. Placebo = 51 m (SD 455) mean. p < 0.001.
Kieffer et al 2001 (24 weeks)	Naftidrofuryl = 98. Placebo = 98.	Constant	Naftidrofuryl = 158.2 m mean. Placebo = 29.9 m mean. p < 0.001
Adhoute et al 1986 (24 weeks)	Naftidrofuryl = 64. Placebo = 54.	Constant	Naftidrofuryl = 201.41 m mean. Placebo = 98.03 m mean. p < 0.02.
Trubestein et al 1984 (12 weeks)	Naftidrofuryl = 54. Placebo = 50.	Constant	Naftidrofuryl = 93 m mean. Placebo = 36 m mean. p < 0.02.

Seven trials that compared pentoxifylline 1200 mg with placebo reported the outcome of pain-free walking distance. Only two trials showed a statistically significant improvement in pain-free walking distance in the pentoxifylline group when compared with the placebo group. Table 11 presents results from published trial reports for pentoxifylline compared with placebo.

Table 11 Pentoxifylline 1200 mg versus placebo (pain-free walking distance)

Trial	Number of participants	Treadmill protocol	Results –change in pain-free walking distance
Creager et al 2008 (24 weeks)	Pentoxifylline = 86. Placebo = 84.	Graded	Pentoxifylline = 34.30%. Placebo = 21.20%. p = not significant.
Dawson et al 2000 (24 weeks)	Pentoxifylline = 232. Placebo = 239.	Graded	Pentoxifylline = 74 m (SD 106) mean. Placebo = 57 m (SD 93) mean. p= 0.07.
Lindgarde et al 1989 (24 weeks)	Pentoxifylline = 76. Placebo = 74.	Constant	Pentoxifylline = geometric mean 80% improvement (SE 12). Placebo = geometric mean 60% improvement (SE 11). p = 0.268.
Porter et al 1982 (24 weeks)	Pentoxifylline = 67. Placebo = 61.	Constant	Pentoxifylline = 47% (SE 10) by geometric mean. Placebo = 26% (SE 9) by geometric mean. 2-sided p = 0.042, 1-sided p = 0.01.
Gallus et al 1985 (8 weeks)	Pentoxifylline = 25. Placebo = 23.	Constant	Pentoxifylline = 55% improvement by geometric mean. Placebo = 26% improvement by geometric mean. Ratio of percentage change from baseline (pentoxifylline/placebo) 1.23 (95% CI 0.86 to 1.77) p < 0.3.
SD = standard deviation. SE = standard error.			

Pain-free walking distance network meta-analysis

The Assessment Group conducted a network meta-analysis including the same trials as in the network of evidence used for the meta-analysis of maximum walking distance. The random effects meta-analysis of the change from baseline in log walking distance showed that treatment with naftidrofuryl 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 and cilostazol compared with placebo resulted in real increases in the percentage change from baseline pain-free walking distance although there was some uncertainty as to the true effect. For further details on the 95% credible intervals see table 30 on page 58 of the assessment report. The Assessment Group stated that variation between studies was moderate, suggesting that the treatment effect varied depending

on the characteristics of the study. Further information on the network meta-analysis is provided on 57–9 of the assessment report.

Ankle brachial pressure index (ABPI)

Nine of the twenty six trials included in the Assessment Group's systematic review reported this outcome. The three trials comparing cilostazol 200mg with placebo showed a statistically significant improvement in ABPI for the cilostazol 200 mg group compared with the placebo group. The three trials comparing naftidrofuryl oxalate 600mg with placebo found no significant difference between the naftidrofuryl oxalate and placebo groups. The two trials comparing pentoxifylline with placebo showed a slight worsening in ABPI for the placebo group and a small improvement for the pentoxifylline group. Both trials found no statistically significant difference between the groups. One trial comparing inositol nicotinate found that there was no significant change in ABPI for either treatment group. For further information on the results of these trials please see tables 31–34 on page 61 of the assessment report.

Mortality

Eighteen (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) of the twenty six trials included in the Assessment Group's systematic review reported this outcome. Across trials no significant differences in mortality rates were reported between treatment groups. The Assessment Group stated that no mortality was attributed to the drugs. The follow-up times were relatively short and only two trials (Dettori et al 1989 and CASTLE by Hiatt et al. 2008) had a follow-up of more than 24 weeks. For further information on the results of these trials please see pages tables 35–9 on pages 62–3 of the assessment report.

Cardiovascular events

Eighteen of the twenty six trials identified by the Assessment Group reported this outcome (eight comparing cilostazol with placebo, 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 treatment groups within trials. The follow-up times were relatively short and only two trials (Dettori et al 1989 and CASTLE by Hiatt et al. 2008) had a follow-up of more than 24 weeks. For further information on the results of these trials please see pages 63–4 of the Assessment Group report.

Adverse events and serious adverse events

Differences in reporting across trials, including that some trials only reported adverse events leading to discontinuation or had unclear clinical criteria for adverse events precluded the Assessment Group undertaking a meta-analysis. Only two trials (Dettori et al 1989 and CASTLE by Hiatt et al. 2008) had a follow-up of more than 24 weeks.

Eight of the cilostazol versus placebo trials included in the Assessment Group's systematic review were included in an analysis by Pratt 2001. The results showed a higher frequency of headaches, diarrhoea, peripheral oedema and palpitations in the group receiving cilostazol than in the group receiving placebo.

In three trials that compared cilostazol with pentoxifylline similar rates of serious adverse events and adverse events were reported in both treatment groups.

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

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 swallowing or gastrointestinal problems.

Further information on adverse events and serious adverse events can be found in tables 40–4 on pages 64–8 of the assessment report.

Health related quality of life evidence

In the twenty six trials included in the Assessment Group's systematic review, different outcome measures were used to estimate quality of life. The SF-36 outcome measure was commonly used and SF-36 data were available for both cilostazol and pentoxifylline. Other outcome measures included in the identified studies were the walking impairment questionnaire (cilostazol and pentoxiflline trials), the claudication outcome measure (cilostazol trials), the vascular quality of life questionnaire (cilostazol trials) and the claudication scale (naftidrofuryl oxalate trial). None of the trials of inositol nicotinate reported health-related quality of life data.

The Assessment Group stated that there is some evidence that cilostazol affects the physical function subscale of SF-36 questionnaire but these results do not appear to translate into overall improvements in quality of life. There is very limited data for naftidrofuryl oxalate and pentoxifylline. Naftidrofuryl oxalate may improve daily living, social life and mood but not anxiety, and pentoxifylline has little effect on health related quality of life.

Summary of clinical effectiveness

Twenty six RCTs were identified that compared the vasoactive drugs with placebo. Three of these trials provided a head-to-head comparison of cilostazol with pentoxifylline and cilostazol, with usual care. The majority of the trials had a short follow-up of no more than 24 weeks. The Assessment Group considered the quality of the trials to be generally good and the population within them to be comparable with the population in UK clinical practice.

For the outcomes of maximum walking distance and pain-free walking distance all patients within the trials tended to show improvement. There was some evidence that cilostazol and naftidrofuryl oxalate significantly improved walking distance outcomes compared with placebo. In most RCTs, when significant improvements for the outcome of maximum walking distance were reported, significant improvements for the pain-free walking distance outcome were also observed.

For the maximum walking distance outcome, most RCTs used constant or graded treadmill protocols (except for the inositol nicotinate trial). Treadmill protocols could not explain the difference in the results of the outcomes reported across the RCTs.

Maximum walking distance and pain-free walking distance meta-analyses were undertaken by the Assessment Group. The meta-analyses showed that treatment with naftidrofuryl oxalate had the greatest effect relative to placebo followed by cilostazol and pentoxifylline. The trials of inositol nicotinate were excluded because they did not provide data in a suitable form for their inclusion in the meta-analysis.

Generally, the adverse events reported for the vasoactive treatment were minor and included headaches and gastrointestinal difficulties. The incidence of serious adverse events including cardiovascular events was not increased and mortality rates had no significant differences between treatment groups. However, it was difficult to assess the impact of vasoactive treatments on these outcomes because of the short follow-up periods. Only two trials with a follow-up of more than 24 weeks were identified (CASTLE study and Dettorri et al. 1989 study).

3.2 Cost effectiveness

3.2.1 Review of published cost-effectiveness studies

The Assessment Group identified two cost effectiveness analyses, one in a published journal paper by Guest et al. (2005) and the other in a conference poster presentation with only an abstract by Ratcliffe (2005).

The publication by Guest et al. (2005) presented the methods and cost-effectiveness analysis comparing cilostazol, naftidrofuryl oxalate and pentoxifylline in people above 40 years of age, who had at least 6 months of intermittent claudication, in the UK. A decision tree was developed to model the management of patients with intermittent claudication over a 24-week period. .In the economic model people, could continue the initial treatment for 24 weeks or discontinue initial treatment People discontinuing initial treatment could either switch to another drug or discontinue drug treatment. Additionally, patients could undergo an angioplasty or bypass surgery. The analysis was carried out from the UK NHS perspective and the outcome of the model was the change in the percentage improvement in maximum walking distance versus the change in cost. Health-related quality of life was not considered in the model.

The effect of each drug in improving mean walking distance for 24 weeks was derived from six published RCTs all of which were identified for inclusion in the Assessment Group's systematic review. Costs included diagnosis of intermittent claudication, drug costs, follow-up visits by the vascular surgeon and/or GP, supervised exercise, angioplasty and bypass surgery. The results showed that treatment with cilostazol compared with naftidrofuryl oxalate increased the percentage improvement (maximum walking distance by 32% (from 57% to 75%) and the costs by 12% (from £801 to £895). Treatment with cilostazol compared with pentoxifylline increases the maximum walking distance by 67% (from 45% to 75%) and reduces costs by 2% (from £917 to £895). Treatment with cilostazol compared with pentoxifylline increases the

maximum walking distance by 27% (from 45% to 57%) and decreases costs by 14% (from £917 to £80).

The Assessment Group identified a number of limitations with the economic analysis. These included: no vasoactive drug comparator; a time horizon of 24 weeks and the effectiveness evaluated only in terms of improvement in mean walking distance.

The abstract by Ratcliffe (2005) briefly described the methods and results of cost-utility analysis of cilostazol compared with placebo in people with intermittent claudication in Scotland. Effectiveness was based on two published 24-week RCTs of cilostazol compared with placebo (not referenced in the abstract). Health related quality of life was measured in the trials using the SF-36. The cost-effectiveness of cilostazol compared with placebo was evaluated in a period of 24 weeks. The incremental cost-effectiveness ratio (ICER) for cilostazol compared with placebo was £12,500 per QALY gained. The Assessment Group was not able to fully evaluate the economic model because no published paper was available.

None of the manufacturers submitted cost-effectiveness evidence.

3.2.2 Assessment Group's model

The Assessment Group developed a de novo Markov economic model to estimate the cost effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline compared with each other and with no vasoactive drugs. The Assessment Group stated that inositol nicotinate was not included in the main analysis because it was not possible to include it in the meta-analysis of maximum walking distance or pain-free walking distance. The cost effectiveness of inositol nicotinate was assessed in a threshold analysis to determine the QALYs needed to be gained to be cost-effective.

Model structure

The model had three distinct health states; vasoactive drug treatment (in which patients received one of the four drugs under evaluation), no vasoactive

drug treatment (in which patients received none of the four drugs or had discontinued) and death. The health states included in the economic model were classified according to whether patients received vasoactive treatment for intermittent claudication. Disease progression through the different Fontaine stages (II, III and IV) was not considered in the economic model because the drugs under evaluation are for symptom relief and they were assumed to have no effect on disease progression or serious cardiovascular events. People in the vasoactive drug treatment health state could improve their quality of life because of treatment effect. People could discontinue drug treatment because of adverse events, deaths or non-compliance. The effectiveness of the drugs under evaluation was assumed to cease after stopping treatment. The model had a cycle of 1 week and a lifetime horizon (up to age 100 years). A diagram of the model structure can be found in figure 2 on page 87 of the assessment report.

Population

The population included in the economic model was people who had stable disease (for at least 3 months, and was an inclusion criteria in most of the RCTs identified) and symptomatic intermittent claudication. Additionally only, people whose symptoms continue despite a period of conventional management (smoking cessation, exercise therapy) were included in the model. A starting age of 66 years was chosen in the model based on the average age of the CASTLE study, because it was the study with the longest follow-up period and the largest number of participants. The economic model did not distinguish between people in primary and secondary care, or severity of disease. However, an exploratory analysis was presented for people who have more severe intermittent claudication and might receive angioplasty after drug discontinuation.

Maximum walking distance and utilities

Only two RCTs (both for cilostazol) included in the Assessment Group's systematic review provided SF-36 quality of life data that could be converted to utilities using published algorithms. The RCTs of naftidrofuryl, pentoxifylline

or inositol nicotinate did not provide sufficient evidence on quality of life to estimate the utility values associated with these drugs. The Assessment Group therefore requested patient-level or summary SF-36 data from the authors of all the identified 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 walking distance and the change in utility scores which could be used to estimate the utility gain for each of the four drugs. The authors of one trial (O'Donnell et al, 2009) comparing cilostazol with no vasoactive treatment provided a complete set of patient-level data (n = 106) for mean walking distance and SF-36 scores.

The SF-36 conversion algorithm (defined by Ara and Brazier, 2008) was used to estimate the utility values at week 0 and 24 (the period of the trial by O'Donnell). The patient-level data were used to test for a correlation between the change in the maximum walking distance outcome and the change in utilities from week 0 to week 24. The correlation coefficient of the absolute difference in mean walking distance on the logarithm scale was estimated to be 0.39. The Assessment Group 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 RCT period. The regression model was applied to all four treatments and to no vasoactive treatment to estimate the absolute changes in utilities given a certain change in mean walking distance from week 0 to week 24 on the logarithm scale. The estimated mean baseline utility values (that is, at week 0) were also calculated using the patient-level data (estimated mean of 0.4838) and were considered by the Assessment Group to reflect the quality of life of patients with stable intermittent claudication in UK clinical practice. Sensitivity analysis was performed to test alternative baseline utility values.

Utility estimates for the general population from Ara and Brazier (2005) were applied using a regression analysis of utility versus age. The age related utility value within the general population was then adjusted to account for the lower average utility associated with people that have intermittent claudication.

The predicted mean utility values for each of the vasoactive treatments and for the no vasoactive treatment are presented in table 12.

Table 12 Utility values

Drug	Mean utility at week 24
No vasoactive drug treatment	0.4873
Cilostazol	0.4973
Naftidrofuryl oxalate	0.5088
Pentoxifylline	0.4919

Mortality

The Assessment Group assumed that all patients will have the same mortality rates because vasoactive treatment is only for the relief of symptoms and will not impact on disease progression. The general population rates were taken from the life tables of England and Wales (Office of National Statistics, 2008). The mortality of the general population was multiplied by the relative risk of mortality of patients with intermittent claudication (1.6) based on a study by Heald et al (2006) of the risk of mortality and cardiovascular disease associated with ankle-brachial pressure index.

Resource use and costs

The costs of the drugs were based on the drug tariff of October 2010. Where there is more than one licensed dose available, the cost of the drug was based upon the doses used with the trials included in the Assessment Group's systematic review. In the base-case, the cost of generic naftidrofuryl was used and, in sensitivity analyses, the impact of the branded price on the ICER was further explored in the model .The Assessment Group assumed that, the costs of diagnosis and follow-up visits for people on vasoactive drugs were the same as for the no vasoactive treatment. This is because all patients will incur the cost of diagnosis and will be followed-up whether they are receiving the vasoactive treatment or not.

Results of Assessment Group's economic analysis

Table 13 shows the base-case results. The base case results suggest that naftidrofuryl oxalate has the lowest additional costs (£298) compared with no vasoactive drug and cilostazol has the highest additional costs (£964); while the additional costs of pentoxifylline is £493. In terms of total quality adjusted life years (QALYs,) naftidrofuryl oxalate is estimated to increase QALYs by 0.049 (from 4.975 to 5.024) compared with no vasoactive drug for PAD. Pentoxifylline is estimated to have the smallest QALY gains (0.009) compared with no vasoactive drug. Cilostazol increases QALYs by 0.019 compared with no vasoactive drug. Overall, the results show that both pentoxifylline and cilostazol are dominated by naftidrofuryl oxalate which has both higher total QALYs and lower additional costs. The incremental cost effectiveness ratio (ICER) associated with naftidrofuryl oxalate compared with no vasoactive drug is estimated to be £6,070.

Table 13 Base-case results

Interventions and comparator	Total costs (additional to no vasoactive drug treatment) (£)	Total QALYs	ICER (£ per QALY gained)	Dominance
No vasoactive drug (baseline technology)	£0	4.975	-	
Pentoxifylline	£493	4.984		Dominated by naftidrofuryl oxalate
Cilostazol	£964	4.994		Dominated by naftidrofuryl oxalate
Naftidrofuryl oxalate	£298	5.024	£6070	
QALY = quality-adjusted life year. ICER = incremental cost-effectiveness ratio.				

Probabilistic sensitivity analysis (PSA)

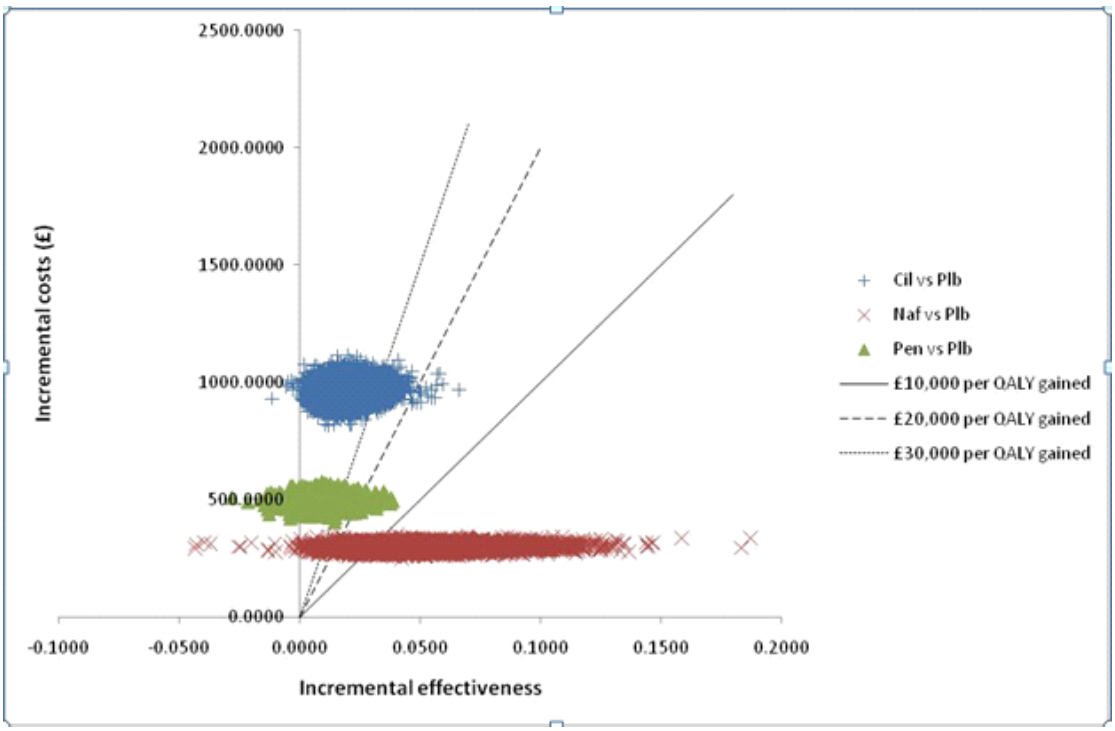
The Assessment Group conducted probabilistic analyses of the following parameters: discontinuation rate for each of the drugs within and beyond 24 weeks, change in mean walking distance, the logarithm scale for the vasoactive drugs and no vasoactive drugs, baseline utilities for patients at week 0 and coefficients (constant and slope) of the regression model to predict the change in utility from the change in MWD. For further information

on the input parameters tested in the PSA analysis please see page 97 of the Assessment Group report.

The cost-effectiveness acceptability curves show that naftidrofuryl oxalate had the highest probability of being most cost-effective above willingness to pay thresholds of £6,000 per quality-adjusted life year (QALY) gained. The probability of cilostazol or pentoxifylline being most cost-effective at any willingness to pay threshold was less than 1%.

The Assessment Group presented the following cost-effectiveness plane, which represents the incremental costs and effectiveness of the vasoactive drugs compared with no vasoactive drugs.

Figure 1 Cost-effectiveness plane showing incremental effectiveness and costs of the vasoactive drugs versus no vasoactive drug (base case)



Cil= cilostazol, plb=placebo, naf=naftidrofuryl, pen=pentoxifylline

The Assessment Group noted that the incremental effectiveness of naftidrofuryl oxalate was associated with the greatest uncertainty (from around −0.05 to around 0.2) and cilostazol was the most robust with the smallest range of uncertainty. The Assessment Group therefore considered that cilostazol might be more effective than naftidrofuryl oxalate but it is unlikely to be considered cost-effective when compared with no vasoactive treatment because of its high costs.

Sensitivity analyses

The Assessment Group undertook a number of univariate sensitivity analyses. These included the following: assumption that the utility value remains the same as when on the drug if discontinuation occurs after 24 weeks; alternative baseline utilities; alternative cost for naftidrofuryl oxalate (price of the generic manufacture used in the base case); shorter time horizon; alternative starting age (55 years of age); alternative long-term discontinuation rates; and angioplasty procedures for patients discontinuing vasoactive treatment within 24 weeks. The results of the sensitivity analyses indicated that the ICERs were relatively insensitive to different baseline utilities, alternative starting ages, and alternative long term discontinuation rates. The exception to ICER estimates were if the effectiveness associated with the vasoactive drugs was assumed to continue over a patient's lifetime when they discontinue the drug after 24 weeks and if patients were assumed to have angioplasty when discontinuing vasoactive treatment within 24 weeks In all of the sensitivity analyses performed by the Assessment Group, both cilostazol and pentoxifylline are dominated or extendedly dominated by naftidrofuryl oxalate.

If the utility value was assumed to remain the same as when on the drug if discontinuation occurs after 24 weeks, the ICER of naftidrofuryl oxalate compared with no vasoactive drug decreased to £1538 per QALY gained (£6070 in the base case). Additionally, if the branded cost for naftidrofuryl oxalate was used and if a time horizon of 24 weeks was used, the ICER of

naftidrofuryl oxalate compared with no vasoactive drug increased to £11,058 and £10,733 per QALY gained, respectively.

Sensitivity analyses that explored the impact of assuming that patients who have more severe intermittent claudication and discontinue the drugs within 24 weeks will receive angioplasty and will improve their quality of life were provided by the Assessment Group. Four different scenarios were explored; the utility associated with angioplasty is equivalent to the utility associated with naftidrofuryl, oxalate the utility is 20% and 40% higher than naftidrofuryl and the utility is equivalent to the general population. The cost of the vasoactive treatment under these sensitivity analyses is set to £1313 (in the base case it was set to £0) because the cost of angioplasty was included. The total QALYs for vasoactive treatment are increased in these scenario analyses because patients were assumed to receive angioplasty first and will experience immediate an improvement in QALYs. The sensitivity analyses showed that the effectiveness of the treatments depend on the assumed utility associated with angioplasty. Naftidrofuryl oxalate dominates pentoxifylline, no vasoactive drug and cilostazol when the utility associated with angioplasty is equivalent to the utility associated with naftidrofuryl oxalate. However, when the utility of angioplasty was assumed to be 20% and 40% higher than the utility associated with naftidrofuryl, no vasoactive drug was associated with the highest total QALYs and the ICERs of no vasoactive drug compared with naftidrofuryl oxalate were less than £20,000 per QALY gained. Cilostazol and pentoxifylline were either dominated by naftidrofuryl oxalate or by no vasoactive drug.

Threshold analyses

The Assessment Group stated that several uncertainties exist in the economic analysis regarding the quality of life evidence, the method for estimating utilities based on the maximum walking distance outcome and the long-term discontinuation rates. The Assessment Group provided threshold analyses (table 14) that estimate the QALYs gained that each of the interventions

should have to be considered cost-effective for willingness to pay thresholds of £20,000 and £30,000 per QALY gained.

Table 14 threshold analyses

Interventions and comparator	Additional costs compared with no vasoactive drug (95% CI)	Required QALYs gained for threshold of £20,000 (95% CI)	Required QALYs gained for threshold of £30,000 (95% CI)
No vasoactive drug (baseline technology)	0	–	–
Cilostazol	£964 (£892 to £1040)	0.048 (0.045 to 0.052)	0.032 (0.030 to 0.035)
Naftidrofuryl oxalate	£298 (£273 to £325)	0.015 (0.014 to 0.016)	0.010 (0.009 to 0.011)
Pentoxifylline	£493 (£454 to £535)	0.025 (0.023 to 0.027)	0.016 (0.015 to 0.018)
Inositol nicotinate	£1695 (£1242 to £2200)	0.085 (0.062 to 0.110)	0.056 (0.041 to 0.073)
CI = confidence interval. QALY = quality adjusted life year.			

These analyses showed that, for naftidrofuryl oxalate to be considered cost-effective compared with no vasoactive treatment, QALY gains of 0.015 and 0.010 were needed for willingness to pay thresholds of £20,000 and £30,000 respectively (and with an additional cost of £298). For pentoxifylline QALY gains of 0.025 and 0.016 for willingness to pay of £20,000 and £30,000 respectively were needed to be considered cost effective compared with no vasoactive treatment (and with an additional cost of £493). Cilostazol was considered cost-effective compared with no vasoactive treatment when it had QALY gains of 0.048 and 0.032 for willingness to pay thresholds of £20,000 and £30,000 respectively (with an additional cost of £964). Inositol needed the highest QALY gained compared with the other treatments to be considered cost effective compared with no vasoactive treatment (additional cost of £1695).

4 Equalities issues

No equalities issues were raised during the scoping exercise or in the assessment report and the manufacturer's submission for this appraisal.

5 Issues for consideration

The majority of the trials included in the Assessment Group's systematic review had a short follow-up period of no more than 24 weeks. There is uncertainty regarding the long-term effectiveness and safety (beyond 24 weeks) of cilostazol naftidrofuryl oxalate, pentoxifylline and inostinol nicotinate.

People with intermittent claudication are at increased risk of cardiovascular events. The Assessment Group's assumed that the vasoactive drugs are for symptom relief and have no impact on the progression of disease or serious cardiovascular events. The Assessment Group stated that the long term safety of cilostazol was tested in a good quality trial and which suggests that there is very little difference between cardiovascular outcomes for cilostazol and placebo. The Assessment Group highlight that are no long term safety studies on naftidrofuryl oxalate, pentoxifylline or inositol nicotinate, and if there was a small increase or reduction in the incidence of cardiovascular events when patients are on these drugs, the results could alter substantially due to the otherwise small impact on costs and quality of life associated with these drugs. What is the Committee's view on the impact of the vasoactive treatment on the cardiovascular events that people with intermittent claudication might experience?

The Assessment Group assumed that the costs of diagnosis and follow-up visits for people on vasoactive drugs were the same as for the no vasoactive treatment. Therefore only the costs of each of the vasoactive drugs were included in the model. The economic evaluation undertaken by Guest et al (2005) included costs of diagnosis of intermittent claudication, follow-up visits, supervised exercise angioplasty and by pass surgery in addition to the drug acquisition cost. Which approach does the Committee consider most appropriate?

The regression model used by the Assessment Group to predict the change of utility from the change of mean walking distance was based only on the

patient level of one study (by O'Donnell et al. 2009) with a small population (n = 106). The underlying assumption of this analysis is that there is the same relationship for all drugs and no vasoactive drug between maximum walking distance and utilities. Direct long term utility data associated with each of the vasoactive drugs would provide less uncertain estimates of cost-effectiveness. A threshold analysis was undertaken to address the uncertainty around the health related quality of life evidence. Does the Committee consider the Assessment Group's method for obtaining the utility values used in the model appropriate? Does the threshold analysis address the uncertainty around the quality of life evidence sufficiently?

The Assessment Group undertook sensitivity analyses assuming that patients who have more severe intermittent claudication and discontinue with the drugs within 24 weeks will receive angioplasty, which showed that naftidrofuryl oxalate was not cost effective compared with no vasoactive treatment. What is the Committee's view on the cost-effectiveness of angioplasty in this subgroup of people?

The Assessment Group did not include inositol nicotinate in the main analysis (but explored in threshold analyses) because it was not possible to estimate the QALY gains associated with inositol nicotinate because of lack of data around maximum walking distance at 24 weeks. What is the Committee's view on this approach?

6 Authors

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December 2010

Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by School of Health and Related Research (ScHARR) Technology Assessment Group, The University of 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 Submissions or statements were received from the following organisations:

I Manufacturer

- Otsuka Pharmaceuticals