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www.sph.nhs.uk/appraisals
Tel: +44 (0)1865 334787
Email: askappraisals@sph.nhs.uk

NHS Salford
Public Health Department
St James's House
Pendleton Way
Salford
M6 5FW

Tel: 0161 212 5634
Fax: 0161 212 4943

National Institute for Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester M1 4BD

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Dear Mr Powell

Regarding: Multiple Technology Appraisal on cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease.

On behalf of NHS Salford, I would like to submit our comments on the appraisal consultation document for the Multiple Technology Appraisal on cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease in the NHS in England and Wales. NHS Salford is in agreement with the appraisal committee's decision that this technology does represent a cost effective use of scarce NHS resources.

- **Naftidrofuryl gave the greatest increase in maximum walking distance relative to placebo**. Twenty-six relevant trials were identified. Amongst trials assessing maximum walking distance, one of two trials of naftidrofuryl, seven of ten trials of cilostazol, two of eight trials of pentoxifylline demonstrated greater improvement in maximum walking distance vs. placebo. One placebo-controlled trial of inositol found no significant benefit. Network meta-analysis conducted by the Assessment Group showed that naftidrofuryl gave the greatest increase from baseline in log mean maximum walking distance (relative increase in log mean maximum walking distance; 60.3% vs. 24.6% with cilostazol and 10.6% with pentoxifylline). The 95% credible intervals demonstrated a significant effect for naftidrofuryl and cilostazol, though the wide intervals implied uncertainty about the size of the true effect.
- **Naftidrofuryl improves other outcomes not considered by specialists to have direct clinical significance to the management of peripheral arterial disease.** Pain-free walking distance was increased relative to placebo in four of five trials of naftidrofuryl, five of ten trials of cilostazol, and two of seven trials of pentoxifylline.

Using network meta-analysis, the maximum benefit was seen for naftidrofuryl (relative increase in pain-free walking distance; 64.2% with naftidrofuryl compared to 13.4% with cilostazol and 9.2% with pentoxifylline). Clinical specialists consider neither pain-free walking distance nor the ankle brachial pressure index to be clinically relevant outcome measures, and the Appraisal Committee agreed that the most appropriate focus should be upon maximum walking distance.

- **There are no major concerns regarding the safety of naftidrofuryl and the vasoactive drugs studied**. The included studies identified no increased rate of serious adverse events with any of the drugs and no mortality or cardiovascular risk relative to placebo. Though the trials were not designed to assess long-term safety, there is post marketing data available and based on all currently available information, there are no major concerns regarding the safety of these drugs.
- **Annual per patient costs for naftidrofuryl would be up to £117.48 for the generic preparation and £214.68 for the branded preparation**. NICE made these estimations based on acquisition drug costs alone using British National Formulary 60 costs (excluding VAT). The best estimate for an average PCT of 300,000 people is a prevalence of 5,766 (62% of 300,000 population x 3.1% prevalence) patients with symptomatic peripheral arterial disease who may be eligible. A preliminary assessment suggests that if the lowest dose generic preparation was used the maximum cost would therefore be in the region of £339,041 per year for a population of 300,000. The potential budget impact for a PCT would depend on the numbers of patients currently receiving vasoactive drugs for peripheral arterial disease, and the preparations currently prescribed. Vasoactive drugs provide symptomatic benefit only and have no effect upon disease progression or survival.
- **There were limitations to the quality of the research**; including a lack of direct comparisons. Three head-to-head trials of cilostazol and pentoxifylline were identified, only one of which demonstrated superiority of cilostazol and was published. All trials were of typically short duration, mostly 24 weeks, though benefit was usually noted by 12 weeks and trial duration was not considered to lead to uncertainty of effect. Some trials had considered the wider pharmacological and lifestyle aspects of care, but few reported the patient's prior response to supportive care and exercise management. Evidence for inositol nicotinate is poor; amongst three RCTs only one examined maximum walking distance and none evaluated pain-free walking distance; this precluded inclusion of this drug in the network meta-analysis. Only one trial of naftidrofuryl could be included in the meta-analysis.

Yours sincerely

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SPH
Solutions for Public Health

Solutions for Public Health
4150 Chancellor Court, Oxford OX4 2GX
Tel: 01865 334700
www.sph.nhs.uk