NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate within their licensed indications for the treatment of intermittent claudication in people with peripheral arterial disease.

Background

Peripheral arterial disease (PAD), also known as peripheral vascular disease, is a condition in which there is blockage of the arteries that carry blood to the legs and arms. The main cause is atherosclerosis. The major risk factors for developing PAD are smoking and diabetes mellitus. Other risk factors include hypertension, hyperlipdaemia, obesity, and a sedentary lifestyle.

PAD can be asymptomatic (Fontaine Classification stage I) or symptomatic (Fontaine Classification stages II to IV). The commonest symptom of PAD is intermittent claudication (stage II), characterized by pain in the legs on walking that is relieved with rest. People with severe PAD experience pain at rest (stage III) and if complete blockage occurs there can be necrosis and gangrene (stage IV).

Intermittent claudication increases with age and is more common in men than women. Approximately, 20% of people aged from 55 to 75 years have evidence of PAD in the legs and a quarter of these people have symptoms. People with intermittent claudication are at increased risk of myocardial infarction and stroke.

A number of interventions are used for the conventional management of intermittent claudication. Treatment should be targeted at reducing the risk from cardiovascular events such as smoking cessation, cholesterol lowering, glycaemic control, weight reduction and blood pressure control. Antiplatelet and statin therapy may be given as a long term prophylaxis of myocardial infarction and stroke. The management of claudication symptoms includes vasodilator therapy (cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate) and exercise therapy (supervised and unsupervised). For people with severe disability or deteriorating symptoms, angioplasty and bypass surgery may be considered as treatment options.

The technology

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

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

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

Inositol nicotinate (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.

Intervention(s)	Cilostazol, naftidrofuryl oxalate, pentoxifylline, inositol nicotinate
Population(s)	People with intermittent claudication due to peripheral arterial disease whose symptoms continue despite a period of conventional management
Comparators	The interventions will be compared with each other within their licensed indications and with: • management of intermittent claudication due to peripheral arterial disease without vasodilator therapy

Outcomes	The outcome measures to be considered include: • maximal walking distance • pain-free walking distance • ankle brachial pressure index • vascular events (including interventions and requirement of hospitalisation) • mortality • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisations.
Related NICE recommendations	Related Technology Appraisals: Technology appraisal No 90, May 2005. Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events. Currently being reviewed. Earliest anticipated date of publication September 2010.