National Institute for Health and Clinical Excellence
Health Technology Appraisal

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Vascular Society of Great Britain and Ireland	In general this is a highly apporpriate topic. PAD is a common condition in middle aged and elderly patients and guidance is needed as to how these medications should be used. The main other intervention of relevance is supervised exercise. It would be worth considering a comparison with supervised exercise if possible.	Comment noted. The inclusion of supervised exercise programmes as a comparator was discussed at the scoping workshop. It was agreed at the scoping workshop that supervised exercise programmes should not be included as a separate comparator because it would be given as an adjunct treatment.
	British Cardiovascular Intervention Society	However, given that many of these patients also have ischaemic heart disease and aortic valve disease, it would be appropriate for the effect of the appraisal treatments on angina status to be considered. Cilastazol can also be used as an agent to protect against stent thrombosis, and so its use in patients also taking aspirin as well as either clopidogrel or prasugrel should also be considered.	Comment noted. The interventions included in the appraisal are being appraised within the remit which specifies only intermittent claudication.

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	Otsuka Pharmaceuticals	Peripheral arterial disease impacts on patients' lives significantly affecting mortality and morbidity. Specifically, the predominant symptom is intermittent claudication affects their walking distance and health related quality of life. Currently, in the NHS, treatment for patients is inconsistent and improved guidance could result in better management and improve the health of patients.	Comment noted.
Wording	Vascular Society of Great Britain and Ireland	Yes.	Comment noted.
	Otsuka Pharmaceuticals	The wording is reflective of the issue of clinical and cost effectiveness that should be considered. A key point is that Pletal's (cilostazol) indication is limited to intermittent claudication while the other molecules tend to have a wider peripheral arterial disease indication	Comment noted. The Methods Guide for Technology Appraisals states that the most appropriate comparator in the care pathway would be one that, at the time of the appraisal, reflects standard care in the NHS for the population for which the technology being appraised has, or is gaining a marketing authorisation
Timing Issues	Vascular Society of Great Britain and Ireland	Moderately urgent.	Comment noted.
	Otsuka Pharmaceuticals	Approximately 5% of over 55s suffer from intermittent claudication which equates to approximately three quarters of a million patients in the U.K. There is variation in practice of patient management of intermittent claudication throughout the U.K.	Comment noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Vascular Society of Great Britain and Ireland	OK.	Comment noted.
	Aberdeen Health Technology Assessment Group	Arterial bypass - might be better to mention both femoro-popliteal and distal bypass. Fem-pop is often not possible in the diabetics because they have more widespread and distal disease, so a long bypass to the foot is sometimes necessary.	Comment noted. The scope is a brief document intending to summarise the key points of the condition and of the technologies.
	Otsuka Pharmaceuticals	Disease etiology, symptomatology, epidemiology, risks and treatments are well summarized in this section.	Comment noted.
The technology/ intervention	Vascular Society of Great Britain and Ireland	OK.	Comment noted.
	Otsuka Pharmaceuticals	Cilostazol is a selective phosphodiesterase type 3 (PDE3) inhibitor. Many of the pharmacological effects of cilostazol are mediated by intracellular cAMP, resulting in platelet aggregation inhibition and vasodilation. In addition, cilostazol also inhibits adenosine uptake and elevates extracellular adenosine levels which may further potentiate the elevation of intracellular cAMP in platelets and smooth muscle cells. Resulting beneficial pharmacological effects of cilostazol are: antiplatelete effect, vasodilatory effect, vascular smooth muscle cell relaxation and inhibition of proliferation and decrease in plasma lipids.	Comment noted. The scope is a brief document intending to summarise the key points of the condition and of the technologies.
Population	Vascular Society of Great Britain and Ireland	OK.	Comment noted.
	Otsuka Pharmaceuticals	The population for Pletal is patients with intermittent claudication without rest pain or peripheral tissue necrosis.	Comment noted. The ‘technology’ section of the scope is consistent with this.

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Comparators	Vascular Society of Great Britain and Ireland	Supervised exercise programs. These could reasonably be described as best alternative care.	Comment noted. The inclusion of supervised exercise programmes as a comparator was discussed at the scoping workshop. It was agreed at the scoping workshop that supervised exercise programmes should not be included as a separate comparator because it would be given as an adjunct treatment.
		There is also some recent work (in press) that statins can improve walking distance. SInce these are commonly used it may be worth considering them also.	Comment noted.
	Aberdeen Health Technology Assessment Group	Walking is a key comparator. The message is always "stop smoking and keep walking.	Comment noted. The ‘comparator ‘section of the scope states ‘management of peripheral arterial disease with out vasodilator therapy’ which is consistent with this.
	Otsuka Pharmaceuticals	All treatments listed are the standard treatments available for Intermittent claudication currently used in the NHS. However, it should be noted that Pletal is the only product with a specific indication for intermittent claudication.	Comment noted.
Outcomes	Vascular Society of Great Britain and Ireland	They seem OK.	Comment noted.

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	Department of Health	We assume that vascular interventions, such as vascular surgery or percutaneous intervention/stenting, are included under the heading 'cardiovascular events' in the outcome measures to be assessed. Whilst they do not appear to be mentioned specifically, we feel that freedom from an intervention is a significant endpoint.	Comment noted. The 'cardiovascular events' outcome has been reworded for clarity as follows: vascular events including interventions and requirement of hospitalisation.
	Aberdeen Health Technology Assessment Group	Amputation should be an outcome, especially amongst the diabetics. The two commonest causes of non-traumatic amputation are smoking and diabetes. Foot ulcer might also be an outcome, especially in diabetics.	Comment noted. The 'cardiovascular events' outcome has been reworded for clarity as follows: vascular events including interventions and requirement of hospitalisation.
		Ankle-brachial pressure index can be misleading in diabetics, because they often have calcification of the middle section of the arterial wall ("Monckeberg's medial calcification") which means that it doesn't compress easily and give a misleading high measurement of blood pressure in the foot. It's the comparison of BP in arm and foot.	Comment noted.
		The reference case timescale should be life, which in this group is curtailed because of cardiac mortality. Though intermittent claudication is often mild, and may improve spontaneously - the series reported in studies are often a more severe spectrum of disease.	Comment noted. The Methods Guide for Technology Appraisals states the time horizon should be sufficiently long to reflect all important differences in the costs or outcomes of technologies being compared.

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	Otsuka Pharmaceuticals	The outcome measures listed capture the most important health related benefits in intermittent claudication. Improvement in maximal and pain-free walking distance (WD) directly address the symptoms of PAD and this should also be reflected in an improvement in the physical components of Quality of Life assessments. When WDs are compared indirectly (not in a direct comparison in the same trial) between treatments across two trials, the following potential varying factors must be taken into consideration: WD measured on flat ground or graded treadmill, grade of treadmill, constant or variable grade. Depending on the grade of the treadmill exercise, WD measured on graded treadmill can be multiplied by the factor 1.5-3 to obtain the corresponding walking distance on flat ground, based on the same amount of energy spent. Comparisons of Treatment Effect over placebo between two treatments evaluated in different trials only give reliable results if either treatment effects for both trials are based on absolute WD or are based on logarithm-transformed WD.	Comment noted. Comment noted. Comment noted. Comment noted. Comment noted.
Economic analysis	Vascular Society of Great Britain and Ireland	As they are the standard ones for NICE I am sure they are appropriate. Certainly at least a 5 year time window needs to be considered. It is important to appreciate that these intervention are to improve quality of life but not extend life in most cases.	Comment noted. The Methods Guide for Technology Appraisals states the time horizon should be sufficiently long to reflect all important differences in the costs or outcomes of technologies being compared.
	Otsuka Pharmaceuticals	The economic analysis appears appropriate, no further comments	Comment noted.
Equality and Diversity	Vascular Society of Great Britain and Ireland	No issues.	Comment noted.

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	Otsuka Pharmaceuticals	No further suggestions	Comment noted.
Other considerations	Otsuka Pharmaceuticals	No further suggestions	Comment noted
Questions for consultation	Otsuka Pharmaceuticals	No further questions	Comment noted
Additional comments on the draft scope.	Aberdeen Health Technology Assessment Group	The statins and clopidrogrel guidances are not really relevant to this MTA. They are there just because most people with PVD also have coronary disease, and many of them die of that. They often have no symptoms of heart disease, so one benefit of diagnosing int claud is that patients may be started on cardioprotective therapy. A recent study is relevant - the POPADAD trial in patients with peripheral arterial disease showed nu benefit of aspirin or anti-oxidants. BMJ 2008:337:a1840, published online October 16th.	Comment noted. Technology appraisal 90 recommended clopidogrel alone (within its licensed indications) for people who are intolerant of low-dose aspirin and either have experienced an occlusive vascular event or have symptomatic peripheral arterial disease. Comment noted. NICE Technology appraisal 94 has been removed from the scope Comment noted.

Comment 4: Regulatory issues

Section	Consultees	Comments	Action

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Remit	Genus Pharmaceuticals	Yes	Comment noted.
	Otsuka Pharmaceuticals	Inclusion of the following wording should be considered	Comment noted.
Current or proposed marketing authorisation	Genus Pharmaceuticals	Current indications for the technology: as stated in the draft scope/remit Planned indications for the technology: no changes planned	Comment noted.
	Otsuka Pharmaceuticals	Current indication: (peripheral arterial disease Fontaine stage II) Planned indications for the technology: not applicable Target date for regulatory submission not applicable Regulatory process: not applicable Anticipated date of CHMP positive opinion: not applicable	Comment noted. Comment noted. Comment noted. Comment noted. Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

- Actavis UK
- Genus Pharmaceuticals Ltd
- Royal College of Nursing
- RICE -Research Institute for the Care of Older People
- Sanofi-Aventis
- Welsh Assembly Government