NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	British Cardiovascular Intervention Society	We were informed recently that NICE did not intend to specifically re-appraise clopidogrel, but it appears that a re-appraisal is considered here. Key issues for patients undergoing primary angioplasty or coronary angioplasty following thrombolysis will be the loading dose of clopidogrel, and the duration of treatment. Clopidogrel use in the context of non-STEMI ACS is being considered by the NICE guidelines development group on this subject. For elective patients undergoing PCI, especially with drug-eluting stents, it is currently recommended that clopidogrel is continued for 1 year until further data become available. BCIS would be interested if this clinical scenario is to be included in this review. In addition, there is a separate ongoing TA on prasugrel and ticagrelor which will be relevant to these patient cohorts.	Comment noted. The use of clopidogrel in combination with aspirin for acute coronary syndromes was considered in TA 80, which will be updated within the clinical guideline. NICE Technology Appraisal No. 90 does not apply to people who require treatment to prevent occlusive events after coronary revascularisation or carotid artery procedures.
	Association of British Neurologists	It would appear appropriate to review the current technology appraisal Number 90 (Clopidogrel and modified release Dipyridamole for the prevention of occlusive vascular events) given the publication of ESPRIT (aspirin versus combination aspirin and Dipyridamole) and PRoFESS (combination aspirin and Dipyridamole versus Clopidogrel) since the last review.	Comment noted, no action required.
	The British Association of Stroke Physicians	It would appear appropriate to review the current technology appraisal Number 90 (Clopidogrel and modified release Dipyridamole for the prevention of occlusive vascular events) given the publication of ESPRIT (aspirin versus combination aspirin and Dipyridamole) and PRoFESS (combination aspirin and Dipyridamole versus Clopidogrel) since the last review.	Comment noted, no action required.

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	British Cardiovascular Society	The guidance in TA90 seems appropriate still. A number of generic versions of clopidogrel have received marketing authorisation and this will lead to a price reduction for clopidogrel when these are marketed, depending on issues with patent for Plavix. It would seem appropriate to delay the review of this topic for a further year rather than conduct this now.	Comment noted. NICE is aware of the CHMP decision on adopting positive opinion by recommending a marketing authorisation for the generic versions of clopidogrel.
	Sanofi – Aventis/Bristol Myers Squibb	It is both appropriate and timely to review the TA 90 guidance as we feel that a substantial body of evidence has accumulated since the original appraisal; PRoFESS (Prevention Regimen for Effectively avoiding Second Strokes): this a multi-centre double blind trial, sponsored by Boehringer Ingelheim which involved 20,332 patients across 695 sites and 35 countries providing the first direct comparison between aspirin and DP and clopidogrel, the drugs considered in TA 90. (Sacco et al. Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke. N Engl J Med 2008; 359). REACH; A large observation registry that included over 60,000 patients, has shown that the totality of risk as defined not only be site of the first event but also by the extent of disease (the overlap symptomatic location) (Steg et al. One-Year Cardiovascular Event Rates in Outpatients with Atherothrombosis. JAMA March 21, 2007 Vol 297, No 11 p1197-1206).	Comment noted, no action required.

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	Department of Health	In our view, there are now more anti-platelet agents such as prasugrel and ticagrelor. Could you please consider extending the scope to include these. We suspect that there will be little or no longer-term data for these agents, but the intention of the guidance would seem to be to determine which anti-platelet agents (or combination of them) should be advised for long term prevention of ischaemic events, and for whom should they be given. We feel therefore that it would seem a more comprehensive guidance if all anti-platelets were reviewed, even if the conclusion were that there are only data for aspirin, dipyridamole & clopidogrel.	Comment noted. The proposed indications prasugrel and ticagrelor are for acute coronary syndromes. Clopidogrel in combination with aspirin for a was appraised in TA 80, and this appraisal will be updated within the ongoing clinical guideline. The use of prasugrel in acute coronary syndromes with PCI is the subject of an ongoing appraisal and an appraisal of ticagrelor for acute coronary syndromes was referred in the 20th wave. It is therefore not appropriate to include these drugs in this review.
Wording	Association of British Neurologists	The wording is appropriate.	Comment noted, no action required.
	The British Association of Stroke Physicians	The wording is appropriate.	Comment noted, no action required.
	British Cardiovascular Society	Satisfactory.	Comment noted, no action required.
Timing Issues	Association of British Neurologists	The timing is appropriate as this evidence is currently in the clinical domain.	Comment noted, no action required.

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	Boehringer Ingelheim	Timing seems appropriate. Assuming that a scope is agreed and a formal invite is sent out in 3-4 months from 20th May (date of receipt of draft scope), based on NICE guidance on minimum time from initiating process to submission by Manufacturer of 15 weeks this would suggest: • Initiating process on 20th August with a submission expected by 3rd December 2009 • Initiating process on 20th September with a submission expected by 3rd January 2010 Both these timelines are in line with the agreed minimum time, as defined in NICE guidance, needed from receipt of the final scope to putting together a submission.	Comment noted.
	The British Association of Stroke Physicians	The timing is appropriate as this evidence is currently in the clinical domain.	Comment noted, no action required.
	British Cardiovascular Society	This is not currently urgent and can be delayed without problem.	Comment noted, no action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Association of British Neurologists	This is appropriate and there is nothing further to add.	Comment noted, no action required.
	The British Association of Stroke Physicians	This is appropriate and there is nothing further to add.	Comment noted, no action required.
	Liverpool Reviews and Implemetation Group	Remove 'disease' from line 8 of 2nd para of 'The technologies'.	Comment noted. The scope has been amended accordingly.
	British Cardiovascular Society	The background should include information about the impact of CYP2C19 genotype on the response to clopidogrel. Patients with reduced CYP2C19 function may not receive the same antiplatelet protection as those with good CYP2C19 function. This information is now included in the US label for clopidogrel.	Comment noted. In the absence of regulatory requirement for genetic testing prior to treatment with clopidogrel, assessing the clinical and cost effectiveness of a strategy including such a test is outside the remit of this appraisal.
The technology/ intervention	Association of British Neurologists	It is appropriate to consider clopidogrel and combination aspirin and dipyridamole versus the comparator.	Comment noted, no action required.
	The British Association of Stroke Physicians	It is appropriate to consider clopidogrel and combination aspirin and dipyridamole versus the comparator.	Comment noted, no action required.

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	British Cardiovascular Society	Clopidogrel binds to the P2Y12 receptor, one of two ADP receptor types on platelets.	Comment noted. The scope is a brief document, intending to summarise the key points of the condition and the technology. This level of detail is not required.
Population	British Cardiovascular Intervention Society	Given other NICE processes, there will be the possibility of confusion if the various guidances do not conform with each other.	Comment noted, no actions required.
	Association of British Neurologists	The population of patients with a history of stroke or transient ischaemic attack is appropriate.	Comment noted, no action required.
	Boehringer Ingelheim	The wording of the patient population should be patients with ischaemic stroke rather than just stroke as at present.	Comment noted. The scope has been amended accordingly.
	The British Association of Stroke Physicians	The population of patients with a history of stroke or transient ischaemic attack is appropriate.	Comment noted, no action required.
	British Cardiovascular Society	This is appropriate.	Comment noted, no action required.
	Sanofi-Aventis/Bristol Myers Squibb	Patients with established atherosclerotic disease in more than one vascular location (multivascular disease; MVD) are a well defined patient population who need to be considered within this appraisal. MVD patients are at increased risk of recurrent cardiovascular events than patients with disease in only one vascular bed; data show that MVD patients have a one in five risk of a major cardiovascular event or hospitalisation within one year (Steg, et al. One-Year Cardiovascular Event Rates in Outpatients with Atherothrombosis. JAMA March 21, 2007 - Vol. 297, No. 11: 1197 - 1206).	Comment noted, no action required. People with multi-vascular disease who are considered at high risk of recurrent occlusive events have been included in the other considerations section of this scope.

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Comparators	Association of British Neurologists	The comparator of aspirin mono therapy is appropriate.	Comment noted, no action required.
	Boehringer Ingelheim	Given the main treatment choice for ischaemic stroke and TIA aspirin tolerant patients being between: Modified-release dipyridamole plus aspirin vs. clopidogrel with aspirin alone being used for those discontinuing treatment, the most appropriate comparison would be using a treatment sequencing model: • 1st line: dipyridamole plus aspirin 2nd line: aspirin versus 1st line: clopidogrel 2nd line: aspirin.	Comment noted, no action required.
	The British Association of Stroke Physicians	The comparator of aspirin mono therapy is appropriate. In addition, aspirin and dipyridamole should be included as a comparator (given the PRoFESS trial).	Comment noted, the scope has been amended accordingly.
	Liverpool Reviews and Implementation Group	Modify aspirin by adding 'low-dose'.	Comment noted. New evidence has emerged since the issue of the NICE guidance comparing MR-dipyridamole to aspirin (75mg-320mg). In this context is considered more appropriate to adopt a wider approach, in terms of aspirin doses, rather than defining it as low-dose aspirin.
	British Cardiovascular Society	The standard treatments are appropriately listed.	Comment noted, no action required.
Outcomes	Association of British Neurologists	The appraisal will look at a wide range of vascular and health related outcomes and these are appropriate.	Comment noted, no action required.

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	The British Association of Stroke Physicians	The appraisal will look at a wide range of vascular and health related outcomes and these are appropriate.	Comment noted, no action required.
	Liverpool Reviews and Implementation Group	Moderate & severe disability (esp. post-stroke) is also an important outcome .	Comment noted. This outcome would be covered by the outcome of health-related quality of life.
	British Cardiovascular Society	Yes.	Comment noted, no action required.
	Sanofi-Aventis/Bristol Myers Squibb	We agree that myocardial infarction (STEMI and NSTEMI), stroke, death, vascular death, adverse effects of treatment including bleeding complications and health-related quality of life are important outcomes. Although unstable angina is an important aspect of ACS to identify it as an outcome will prove difficult as there are no available data which consider this as an endpoint. In addition unstable angina should not be considered as an outcome as it acts as a surrogate marker/predictor for a myocardial infarction.	Comment noted, no action required. Unstable angina is a predictor of MI, but it is also a clinical event in itself and not merely a surrogate marker. All acute coronary events are relevant to this appraisal.
Economic analysis	Association of British Neurologists	Appropriate.	Comment noted, no action required.
	The British Association of Stroke Physicians	Appropriate.	Comment noted, no action required.
	British Cardiovascular Society	See above re generic clopidogrel.	Comment noted. NICE is aware of the CHMP decision on adopting positive opinion by recommending a marketing authorisation for the generic versions of clopidogel.

Section	Consultees	Comments	Action
Equality and Diversity	Association of British Neurologists	No further comments.	Comment noted, no action required.
	The British Association of Stroke Physicians	No further comments.	Comment noted, no action required.
	British Cardiovascular Society	No comment.	Comment noted, no action required.
Other considerations	Association of British Neurologists	It would appear appropriate to consider the effectiveness of clopidogrel in patients with multi-vascular disease at high risk of recurrent occlusive vascular events.	Comment noted, no action required.
	The British Association of Stroke Physicians	It would appear appropriate to consider the effectiveness of clopidogrel in patients with multi-vascular disease at high risk of recurrent occlusive vascular events.	Comment noted, no action required.
	Liverpool Reviews and Implementation Group	It is not clear how this group differs from the main Population – is it not just a subgroup? Why is it special compared to other subgroups? Can it be defined clearly as it seems rather vague?	One of the future research recommendations included in the current NICE TA 90 was the examination of the effectiveness of clopidogrel in people with polyvascular disease who are at high risk of recurrent OVEs.
	British Cardiovascular Society	No comment.	Comment noted, no action required.
Questions for consultation	Association of British Neurologists	No further questions to add.	Comment noted, no action required.

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	The British Association of Stroke Physicians	No further questions to add.	Comment noted, no action required.
	Sanofi-Aventis/Bristol Myers Squibb	The subgroup suggested in “other considerations” are appropriate.	Comment noted, no action required.
Additional comments on the draft scope.	Royal College of Physicians	There is a need to consider the short-term use of aspirin + clopidogrel after transient ischaemic attack (TIA) as used in the EXPRESS study (Lancet, Volume 370, Issue 9596, Pages 1432 - 1442, 20 October 2007) . Also the combination of aspirin + dipyridamole as a standard comparator because of the PRoFESS study (N Engl J Med. 2008 Sep 18;359(12):1238-51). We also believe it is important that NICE re-visit the previous recommendation that MR Dipyridamole should be stopped after 2 years because this is causing a lot of confusion.	1) Comment noted. 2)Comment noted, the scope has been amended accordingly. 3) The duration of treatment with MR dipyridamole and aspirin, will be considered if the evidence allows. The other considerations section of the draft scope has been amended accordingly.
	Sanofi-Aventis/Bristol Myers Squibb	Evidence from a major new study suggests that Extended Release Dipyridamole plus Aspirin had significantly more major haemorrhagic events and discontinuations than clopidogrel monotherapy, and that Extended Release Dipyridamole plus Aspirin is not more effective than clopidogrel monotherapy in preventing further events in stroke patients (Sacco et al. Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke. N Engl J Med 2008;359). Clopidogrel has been shown to be cost-effective compared to aspirin specifically in a group of MVD patients who have had a prior MI and then have a stroke or PAD (Stevenson et al 'Clopidogrel is Cost-effective compared with aspirin in UK patients with Multivascular Disease. ISPOR, Toronto 3 - 7 May 2008).	Comment noted, no action required.

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Current or proposed marketing authorisation	Boehringer Ingelheim	Dipyridamole 200mg and 25 mg aspirin (Asasantin Retard) 1 capsule twice daily - Secondary prevention of ischaemic stroke and transient ischaemic attacks. Persantin Retard (dipyridamole 200mg) 200mg twice daily - Secondary prevention of ischaemic stroke and transient ischaemic attacks (used alone or with aspirin).	Comment noted, no action required.

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

Bayer Healthcare
Royal College of Nursing
Teva UK
The Research Institute for the Care of Older People
Welsh Assembly Government