

**National Institute for Health and Clinical Excellence**  
**Prasugrel for the treatment of acute coronary artery syndromes with percutaneous coronary intervention**

**Comment 1: the draft remit**

<b>Section</b>	<b>Consultees</b>	<b>Comments</b>	<b>Action</b>
Appropriateness	British Cardiovascular Society	My one concern is that this appraisal may be occurring too early. Currently there are only 2 randomised studies comparing standard therapy with clopidogrel versus prasugrel. Is this enough to come to a valid conclusion?	The NICE single technology appraisal (STA) process seeks to produce guidance on a technology as soon as possible after it has received marketing authorisation. Guidance is only produced by NICE if marketing authorisation is granted.
	British Institute of Radiology	This is an early topic to refer to NICE, since existing data are suggestive but not conclusive of improved outcome in ACS sub-groups due to equivalent increase in bleeding risk to reduction in cardiovascular events.	The NICE single technology appraisal (STA) process seeks to produce guidance on a technology as soon as possible after it has received marketing authorisation. Guidance is only produced by NICE if marketing authorisation is granted.
	Bristol-Myers Squibb Pharmaceuticals Ltd /Sanofi-Aventis Ltd	It is appropriate for this topic to be referred for an appraisal by NICE.	Comment noted.
	Eli Lilly and Company Limited and Daiichi-Sankyo	It is appropriate for this topic to be referred to NICE.	Comment noted.
Wording	British Cardiovascular Society	The first paragraph entitled "Technology" should be clearer that the comparison is between aspirin and clopidogrel versus aspirin plus prasugrel	Scope amended.
	British Institute of Radiology	Appropriate	Comment noted.

## Appendix C - Summary form

Section	Consultees	Comments	Action
	Bristol-Myers Squibb Pharmaceuticals Ltd /Sanofi-Aventis Ltd	The wording should specifically capture that prasugrel may not be appropriate for all patients with acute coronary syndromes with percutaneous coronary intervention, and may be only appropriate for patients with known coronary anatomy suitable for coronary intervention.	The remit now states that prasugrel will be appraised within its licensed indication (when known). An appraisal of prasugrel would examine the groups for whom prasugrel is appropriate or inappropriate within the limits of the licence.
	Eli Lilly and Company Limited and Daiichi-Sankyo	Appropriate	Comment noted.
Timing Issues	British Institute of Radiology	Non-urgent	Comment noted.
	Bristol-Myers Squibb Pharmaceuticals Ltd /Sanofi-Aventis Ltd	Suggested timing for evidence submission has not been communicated at this stage. However, it would be most appropriate for the appraisal to take place after the TRILOGY results are available.	The TRILOGY study focuses a different group of patients and is not within the remit of this appraisal.
	Eli Lilly and Company Limited and Daiichi-Sankyo	We will be in a position to submit evidence to NICE once the CHMP has issued their positive opinion anticipated [REDACTED] (confidential). With this in mind the earliest possible submission date to [REDACTED].	Comment noted.

**Comment 2: the draft scope**

<b>Section</b>	<b>Consultees</b>	<b>Comments</b>	<b>Action</b>
Background information	British Cardiovascular Society	There is no specific reference list but the major background data is derived from the TIMI 38 study.	Comment noted.
	British Institute of Radiology	Comment on long-term management of ACS ignores the use of ACE inhibitors.	The information provided in the scope is not intended to be exhaustive. The scope provides an overview of the management of ACS and includes reference to more detailed NICE documentation.
The technology/ intervention	British Cardiovascular Society	Except the point about aspirin as stated above	Scope amended.
	British Institute of Radiology	Add description of putative advantages over existing therapy	An appraisal considers the advantages/disadvantages of a technology. This information is not included in a scope.
	Eli Lilly and Company Limited and Daiichi-Sankyo	Prasugrel is a novel ORAL platelet inhibitor. Initial results from pivotal phase 3 trial (TRITON-TIMI 38) are now published and stakeholders should be aware of this: Wiviott SD, Braunwald E, McCabe CH (2007) Prasugrel versus clopidogrel in patients with Acute Coronary Syndromes. N Eng J Med ; 357: 2001-15	Scope amended.
Population	British Cardiovascular Society	Appropriate	Comment noted.
	British Institute of Radiology	Appropriate	Comment noted.

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	Bristol-Myers Squibb Pharmaceuticals Ltd /Sanofi-Aventis Ltd	The appropriate patient population in which prasugrel should be appraised should be PCI patients presenting with NSTEMI, with a known coronary anatomy and PCI managed STEMI patients <12hr presentation. Non-PCI managed ACS patients should be excluded as they have not been studied. PCI patients with a known coronary anatomy were enrolled in the main registration trial, TRITON.	The population is defined as patients presenting with ACS who are to be managed with PCI, in line with information from the pivotal phase 3 clinical trial and the planned indication for prasugrel.
	Eli Lilly and Company Limited and Daiichi-Sankyo	See Issues for Consideration below	Comment noted.
Comparators	British Cardiovascular Society	Aspirin + clopidogrel versus aspirin + prasugrel	Comparators changed to aspirin in combination with clopidogrel versus aspirin in combination with prasugrel
	British Institute of Radiology	Aspirin plus clopidogrel Aspirin	Comparators changed to aspirin in combination with clopidogrel versus aspirin in combination with prasugrel. Aspirin monotherapy has been removed as it is not a standard treatment for ACS.

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	Bristol-Myers Squibb Pharmaceuticals Ltd /Sanofi-Aventis Ltd	<p>Clopidogrel use in ACS is endorsed by multiple guidelines internationally (SIGN, NICE, ESC, ACC/AHA) as standard of care in combination with aspirin and is the ideal thienopyridine comparator for prasugrel.</p> <p>The treatment pathway in the TRITON trial, as defined in the trial protocol, does not correspond to current clinical practice in the UK or in Europe. The practice of determining coronary anatomy prior to loading with clopidogrel is not recommended by ESC guidelines: in fact this practice is discouraged. Loading on clopidogrel is advised as soon as ACS is diagnosed, as long as there are no contraindications. The loading dose protocol timing for clopidogrel used in TRITON is not consistent with the evidence from CURE, PCI-CURE, CREDO, CLARITY etc.</p> <p>Higher clopidogrel loading doses (i.e 600mg) have been studied and shown to be superior to 300mg in terms of event reduction outcomes (ARMYDA trial &amp; Cuisset et al. 2006 J Am College of Cardiology). Although currently off-label, the 600mg loading dose of clopidogrel is common in clinical practice and the efficacy and safety of such a regime is being confirmed in the CURRENT registrational trial expected to report at the end of 2008.</p>	Comments noted.
	Eli Lilly and Company Limited and Daiichi-Sankyo	<p>Clopidogrel plus aspirin is the appropriate comparator.</p> <p>Aspirin monotherapy should be removed since this is not a routine treatment for ACS during PCI.</p>	Comparators changed to aspirin in combination with clopidogrel versus aspirin in combination with prasugrel. Aspirin monotherapy has been removed.
Outcomes	British Cardiovascular Society	I think you should add revascularisation and stroke specifically	Need for revascularisation has been added to the outcomes. Incidence of stroke has not been added as it falls under adverse effects of treatment.
	British Institute of Radiology	Appropriate	Comment noted.

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	Bristol-Myers Squibb Pharmaceuticals Ltd /Sanofi-Aventis Ltd	<p>Over the 15 month TRITON study, prasugrel showed a significant 19% relative risk reduction in the combined primary endpoint over delayed loading dose clopidogrel on a background of ASA. However, this difference in efficacy between prasugrel and delayed loading dose clopidogrel occurs primarily at the beginning of the trial, and may be overestimated because the 300mg loading dose of clopidogrel was delayed. This initial dose was given insufficient time to achieve a steady state and in contrast to the previously demonstrated evidence base regarding loading dose timing. The same issue is relevant to the stent thrombosis results.</p> <p>Mortality is the most important outcome to be measured. Indeed, it should be noted that in the TRITON trial, overall mortality did not differ significantly across treatment arms as the benefit was offset by a significant increase in TIMI major, life threatening, CABG related and fatal bleeds.</p> <p>If the treatment algorithm within TRITON were to be adopted in the UK, there would need to be considerable investment in infrastructure to allow for rapid cardiac catheterisation and subsequent revascularisation surgery, as seen in the US. However, this treatment strategy should also take into account the very high rate (HR 4.73) of TIMI major bleeding experienced by patients on prasugrel who then proceeded to have a CABG, which was not included in the main safety results of the trial.</p> <p>It should also be noted that the use of TIMI major bleeding as a measure of bleeding outcomes is much less severe than the major bleeding measures used in the CURE study. Therefore, it should be noted that the adverse outcomes demonstrated in TRITON with prasugrel are likely to be underestimated in comparison to clopidogrel.</p>	Comments noted.
Economic analysis	British Institute of Radiology	Appropriate	Comment noted.
	Bristol-Myers Squibb Pharmaceuticals Ltd /Sanofi-Aventis Ltd	Use of glycoprotein IIb/IIIa inhibitors should be included within the economic analysis as these are costly therapies that are used in differing amounts by patients treated with clopidogrel compared with prasugrel. The cost of angiograms should also be included, as more angiograms are likely to be needed to establish the coronary anatomy for each patient treated with prasugrel.	All relevant costs will be included in the economic analysis.

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Equality	British Cardiovascular Society	It will be difficult given the paucity of current data to be definitive about sub groups who may benefit more than others	Comment noted.
Other considerations	British Institute of Radiology	Application to sub-groups including: Previous cerebrovascular disease Age over 75yrs Low weight High risk, including diabetes and renal impairment	A sentence on subgroups has been added to the scope: 'Where the evidence allows subgroups at high risk of adverse events or which have the potential for enhanced benefit will be considered.'
Questions for consultation	British Cardiovascular Society	It will be difficult given the paucity of current data to be definitive about sub groups who may benefit more than others	Subgroups at high risk of adverse events or which have the potential for enhanced benefit will only be considered if the evidence allows.
	Bristol-Myers Squibb Pharmaceuticals Ltd /Sanofi-Aventis Ltd	Unlike clopidogrel, which is licensed across the spectrum of ACS, prasugrel has only been studied in carefully selected patients with a known coronary anatomy. Due to safety concerns, a post hoc analysis was performed to determine whether any groups within the TRITON population would not benefit on prasugrel, as compared with delayed loading dose clopidogrel. The first group was patients with a past history of stroke or TIA, for whom there was a suggestion of harm. Patients over 75 (based on BCIS returns, 31% of patients who underwent PCI in the UK were above the age of 71) and those who weighed under 60Kg were also found to derive no benefit from prasugrel. However, it should be noted that this was a post hoc analysis, that was not specified prior to randomisation, and the implication that the remaining patients would benefit even more has to be considered very carefully as with all on-treatment analyses.	Comment noted.
	Eli Lilly and Company Limited and Daiichi-Sankyo	We are currently in the process of fully evaluating the clinical benefit risk and cost effectiveness of all the patient subgroups as part of our overall regulatory submission.	Comment noted.

Section	Consultees	Comments	Action
Additional comments on the draft scope.	British Cardiovascular Society	<p>I do wonder if this is a bit early.</p> <p>Of much more general interest (possibly to be incorporated into the ACS review is "In patients with NSTEMI beyond what time frame from the index admission is invasive investigation and revascularisation still evidence based?"</p>	<p>The NICE single technology appraisal (STA) process seeks to produce guidance on a technology as soon as possible after it has received marketing authorisation. Guidance will only be produced by NICE if marketing authorisation is granted.</p> <p>This is not within the remit of the appraisal received by the Department of Health.</p>

**Comment 4: Regulatory issues**

Section	Consultees	Comments	Action
Remit		Appropriate	Comment noted.
Current or proposed marketing authorisation	Eli Lilly and Company Limited and Daiichi-Sankyo	<p>Planned indications: Patients undergoing percutaneous coronary intervention for Acute Coronary Syndromes.</p> <p>Target date for regulatory submission: [REDACTED]</p> <p>Regulatory process: [REDACTED]</p> <p>Anticipated CHMP opinion [REDACTED]</p> <p>Regulatory approval [REDACTED]</p> <p><u>All references to CHMP Opinion and Approval timings should be regarded as commercial in confidence</u></p>	Comment noted.

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

Department of Health  
NHS Quality Improvement Scotland

NPHS Wales  
Research Institute for the Care of Older People