National Institute for Health and Clinical Excellence

Ticagrelor for the treatment of acute coronary syndromes

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	AstraZeneca	AstraZeneca believes the Institute should review ticagrelor as close to launch as possible as the indication of ACS falls within the government's priority area of cardiovascular disease.	Comment noted
	Oxfordshire PCT	We agree that this is an appropriate technology for referal	Comment noted
	RCN	We feel that this topic is very approproate in light of number of patients.	Comment noted
	Sanofi Aventis / BMS	It is appropriate for this topic to be referred for an appraisal by NICE.	Comment noted
	Department of Health	No comments	Comment noted
Wording	AstraZeneca	No comments	Comment noted
	Oxfordshire PCT	No comments	Comment noted
	RCN	We would prefer to have an identified measure for health related quality of life identified; for example EQ-5D, which could allow international analysis	The NICE reference case specifies that health related quality of life should be reported using a choice based method such as the EQ5D. Please refer to section 5.4. of the Guide to the Methods of Technology Appraisal.

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	Sanofi Aventis / BMS	No comments	Comment noted
	Department of Health	No comments	Comment noted
Timing Issues	AstraZeneca	No timing provided within current documentation. [redacted]	Comment noted
	Oxfordshire PCT	Timing is appropriate	Comment noted
	RCN	As existing interventions have been deemed efficient and cost effective, it is felt that the timing routine is not urgent.	Comment noted
	Sanofi Aventis / BMS	No comments	Comment noted
	Department of Health	No comments	Comment noted
Additional comments on the draft remit	AstraZeneca	No comments	Comment noted
	Oxfordshire PCT	No comments	Comment noted
	RCN	No comments	Comment noted
	Sanofi Aventis / BMS	No comments	Comment noted
	Department of Health	No comments	Comment noted

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	AstraZeneca	No comments.	Comment noted
	Oxfordshire PCT	Yes	Comment noted
	RCN	No comments	Comment noted

Section	Consultees	Comments	Action
	Sanofi Aventis / BMS	No comments	Comment noted
	Department of Health	No comments	Comment noted
The technology/ intervention	AstraZeneca	The description is mainly correct - however, the description of the clinical trial contains inaccuracies. The study comparing clopidogrel with ticagrelor (PLATO) includes patients with a history of both CABG and PCI - it is therefore not correct to state that the population refers to 'ACS who had not previously undergone revascularisation'. The wording should be amended to, 'It has been studied in clinical trials versus clopidogrel for patients who may have undergone revascularisation in the past.'	Following consultation this section of the scope has been amended accordingly.
	Oxfordshire PCT	Yes	Comment noted
	RCN	No comments	Comment noted
	Sanofi Aventis / BMS	No comments	Comment noted
	Department of Health	No comments	Comment noted
Population	AstraZeneca	This is incorrect. As noted above, the PLATO trial included patients who may have previously undergone revascularisation, hence this statement should be amended to read, 'Patients presenting with ACS who may or may not have previously undergone revascularisation.'	Following consultation on the scope the population has been amended to state ‘Patients presenting with ACS irrespective of whether they have undergone revascularisation’.

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	Oxfordshire PCT	Our understanding is that the expected place in theapy for ticagrelor would be in patients who have not responded to therapy with clopidogrel	Technologies are appraised within their licensed indications, and it is not anticipated that ticagrelor will be licensed for second line treatment of patients who have not responded to clopidogrel.
	RCN	We would be interested to determine the impact of this treatment on patients with comorbid chronic conditions who are receiving the alternative interventions currently.	Comment noted
	Sanofi Aventis / BMS	No comments	Comment noted
	Department of Health	We note that the scope confines itself to patients with acute coronary syndrome "who have not undergone previous revascularisation". We are assuming that this is because the trial data use them as the population. In our view however, it could exclude a large number of potentially appropriate recipients, namely those who have had previous revascularisation.	Following consultation on the scope the population has been amended to state 'Patients presenting with ACS irrespective of whether they have undergone revascularisation'.
Comparators	AstraZeneca	Whilst the patient population can be split into patients who may or may not undergo PCI, with reference to the comparator 'prasugrel plus aspirin' it should be noted that the patient populations and trial designs within the TRITON and PLATO trials were very different (PLATO was a much broader patient population which included medically-treated patients as well as revascularisation, whereas in TRITON all patients underwent PCI [including STEMI and N-STEMI patients]). Hence it may be difficult to fully identify a similar patient population that could be reasonably compared between PLATO and TRITON.	Following consultation on the scope the population has been amended to state 'Patients presenting with ACS irrespective of whether they have undergone revascularisation'.
	Oxfordshire PCT	No comments	Comment noted
	RCN	This treatement can be viewed as best alternative care.	Comment noted

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	Sanofi Aventis / BMS	When comparing to clopidogrel in patients being managed via PCI, patients in the PLATO trial (http://clinicaltrials.gov/ct2/show/NCT00391872? term =plato& cntry 1 NS% 3AGE&rank =1)will be loaded with an additional 300mg pre PCI (600 mg). This currently off label dose is being investigated in the CURRENT trial (Am heart J 2008;0:1-9.e.1) due to report in March 09, with subsequent filing later in the year. We know from the ALBION PK studies (Montalescot et al. JACC 2006;48:931-8) that it takes about 2-6 hours for a 600 mg dose of clopidogrel to achieve maximal IPA(Inhibition of platelet activity) and therefore loading the additional 300mg in the PLATO study pre PCI, may not be allowing optimal use of clopidogrel. When comparing to prasugrel, it is important to note that no head to head studies have been carried out between ticagrelor and prasugrel. Indirect comparisons using studies with non-clinical endpoints(% IPA) can be misleading as high IPA do not necessarily correlate with clinical outcomes. Indeed in the TRITON-TIMI 38 study, this high degree of IPA was not only accompanied by a RRR in the primary endpoint, but also significant increases in major, life threatening and fatal bleeds for the whole cohort. In subsequent sub-analyses, 2 subgroups of patients from TRITON have been found to benefit without significant increases in major bleeds, namely diabetic(Wiviott et al Circulation. 2008;118:1626-1636) and Primary PCI STEMI patients(Montalescot. Data presented at ESC 08). However, these have also highlighted the lack of a net clinical benefit in the majority of the TRITON population, i.e. non-diabetic and patients with UA or NSTEMI.	The comparators section of the scope is intended to be a brief summary of the potential comparators which may be appropriate for the analysis. Please see section 2 of the Guide to the Methods of Technology Appraisal. http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459
	Department of Health	No comments	Comment noted

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Outcomes	AstraZeneca	AstraZeneca believes that the primary endpoint from the PLATO study should drive the outcomes to be measured. For example, death due to vascular causes, MI and stroke is a primary endpoint in the PLATO trial. Secondary endpoints from PLATO include: Numerous arterial thrombotic events Thrombotic cardiovascular events (fatal and non-fatal) Recurrent ischaemia The draft scope suggests 'need for revascularisation' as a potential outcome. This particular outcome will be difficult to assess as in the PLATO study all patients with STEMI will receive revascularisation, whilst for patients with NSTEMI or unstable angina it will be up to the investigators' discretion whether they will be medically managed or revascularised.	Following the scoping workshop consultees agreed that the outcomes defined in the scope were appropriate, and no changes were necessary.
	Oxfordshire PCT	Yes	Comment noted
	RCN	This depends on the HR-QOL tool being used. If EQ-5D is used, this will allow comparisons. These may be restricted if the EQ-5D is not the tool being used.	The NICE reference case specifies that health related quality of life should be reported using a choice based method such as the EQ5D. Please refer to section 5.4. of the Guide to the Methods of Technology Appraisal.

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	Sanofi Aventis / BMS	As antiplatelet agents get more and more potent, it is important to evaluate not just efficacy but the benefit/risk ratio. It should be noted that the bleeding definitions from the PLATO trial are slightly different from the CURE*/CLARITY**/TRITON studies and this should be taken into account. For example, a reanalysis of the CURE study to evaluate safety in terms of the TIMI bleeding score did not show a significant increase associated with addition of clopidogrel. *New England Journal of Medicine 2001;345:494-502 ** Sabatine et al. New England Journal of Medicine 2005;352:1179-1189	The outcomes section of the scope is intended to be a brief summary of the principle health outcome measures appropriate for the analysis. Please see section 2 of the Guide to the Methods of Technology Appraisal. http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459
	Department of Health	No comments	Comment noted
Economic analysis	AstraZeneca	No comments	Comment noted
	Oxfordshire PCT	No comments	Comment noted
	RCN	This should allow for a follow-up of 18 months or more.	Comment noted
	Sanofi Aventis / BMS	No comments	Comment noted
	Department of Health	No comments	Comment noted
Equality and Diversity	AstraZeneca	No comments	Comment noted
	Oxfordshire PCT	No comments	Comment noted
	RCN	If no-one is excluded on the basis of race, disability, religion and/or sexual orientation then no equality issues are presented.	Comment noted

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	Sanofi Aventis / BMS	No comments	Comment noted
	Department of Health		Comment noted
Other considerations	AstraZeneca	No comments	Comment noted
	Oxfordshire PCT	If ticagrelor is to be used when clopidogrel therapy has been considered to fail we would like to see treatment failure defined within guidance	Technologies are appraised within their licensed indications, and it is not anticipated that ticagrelor will be licensed for second line treatment of patients who have not responded to clopidogrel.
	RCN	No comments	Comment noted

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	Sanofi Aventis / BMS	The study population for PLATO excludes patients who have had previous revascularisation. This ACS population is at high risk of further events and in the UK, about 26% of patients presenting with ACS will have had a previous MI(MINAP 2006 report). The ESC EuroHeart survey reported that at 30 days, about 16% of patients (n=828) discharged after an ACS episode had to be readmitted with the majority being cardiac related, needing coronary angiography, PCI, CABG or other cardiac surgery(Euro Heart survey investigators Eur Heart J2006 27:2285-93). Therefore, the PLATO study is not looking at a real world population where this drug may be used in patients with previous resvacularisation. The risk benefit ratio has not been studied in that particular population. It is also important to note that in the CURE study, patients with a history of revascularisation(n=2246) had a 6% actual risk reduction in the primary endpoint compared to 2.1% in the overall group(n=12562)(CURE investigators, NEJM 2001 345:494-502) . In the phase 2 study of AZD6140, DISPERSE-2(Cannon et al JACC 50:1844-51 2007), a specific side effect of dyspnoea was noted, in about 10% of patients at the lower dose(90mg BD) and 16% in the higher dose(180 mg BD). In the context of ACS, this can obviously be a worrying symptom that could lead to unnecessary escalation of treatment. This SAE will be monitored closely in PLATO and it will be important to see if this side effect manifests itself significantly in the larger phase 3 program and more importantly, if it leads to discontinuation of therapy.	Comment noted. Following consultation on the scope the population has been amended to state 'Patients presenting with ACS irrespective of whether they have undergone revascularisation'.
	Department of Health	No comments	Comment noted
Questions for consultation	AstraZeneca	No comments	Comment noted
	Oxfordshire PCT	No comments	Comment noted

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	RCN	Many of these men will be working age. Excluding loss of income and salary and only determining the NHS perspective may not reflect the economic aspect sufficently. There needs to be some consideration given to potential diffferences in return to work rates.	Productivity costs are not included reference case and non-reference case analyses. Please refer to section 5.2.10 of the Guide to the Methods of Technology Appraisal.
	Sanofi Aventis / BMS	No comments	Comment noted
	Department of Health	No comments	Comment noted
Additional comments on the draft scope.	AstraZeneca	No comments	Comment noted
	Oxfordshire PCT	No comments	Comment noted
	RCN	No comments	Comment noted
	Sanofi Aventis / BMS	No comments	Comment noted
	Department of Health	No comments	Comment noted

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

Eli Lilly
NHS QIS
RICE
Welsh AG
NPHS
Royal Pharmaceutical Society