National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction [ID813]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	AstraZeneca	AstraZeneca believes the Institute should review ticagrelor as close to launch as possible as the indication for preventing atherothrombotic events after an MI falls within the government's priority area of cardiovascular disease.	Thank you for your comment. This topic has been referred to NICE by the Department of Health refers the topic to NICE. Please see section 2.5.19 of the NICE guide to the process of technology appraisal for further details. http://www.nice.org.uk/article/pmg19/chapter/2-selection-of-technologies#developing-the-remit-and-scope
	United Kingdom Clinical Pharmacy Association	Yes - appropriate to refer for appraisal	Thank you for your comment. No action required.

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	(UKCPA) Cardiac Group		
Wording	AstraZeneca	Please amend the remit to more accurately reflect the expected indication: To appraise the clinical and cost effectiveness of ticagrelor within its marketing authorisation to reduce atherothrombotic events in adults with a history of myocardial infarction (MI occurred at least one year ago) and are at high risk of developing an atherothrombotic event	Thank you for your comment. The remit has been updated following positive opinion by the Committee for Medicinal Products for Human Use (CHMP).
	United Kingdom Clinical Pharmacy Association (UKCPA) Cardiac Group	The current marketing recommends treatment for up to 12 months - as such the scope of the technology appraisa in terms of extended duration of use falls outside of the MA. Also - is the scope too narrow? Sould the question actually relate to the use of all P2Y12 inhibitors over an extended duration and include clopidogrel, prasugrel and ticagrelor? So, is the use of long term dual antiplatelet therapy following the index event justified and if so, which is the preferred second agent?	Thank you for your comment. The remit has been updated following positive opinion by the Committee for Medicinal Products for Human Use (CHMP). NICE can only appraise a technology within its marketing authorisation and therefore prasugrel and clopidogrel cannot be included as interventions for this appraisal. Clopidogrel plus aspirin has been included as a

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			comparator because of its use in clinical practice.
Timing Issues	United Kingdom Clinical Pharmacy Association (UKCPA) Cardiac Group	Topical - but perhaps not clinically urgent	Thank you for your comment. No action required.
Additional comments on the draft remit	United Kingdom Clinical Pharmacy Association (UKCPA) Cardiac Group	The reduction in ischaemic events (1%) is offset by an increase in TIMI major bleeding (1.64%) as shown in PEGASUS. The trial doesn't reflect UK practice - once patients are discharged from hospital, their management is overseen by their GP - patients are either referred back into secondary/tertiary care on symptom reoccurence or will present again following another adverse cardiac event - we wouldn't retrospectively seek out 'high risk' patients. Consideration should be given to the DAPT study in which long term prasugrel/clopidogrel was investigated as the second antiplatelet agent - would it be appropriate to assume that the same clinical benefits can be derived from clopidogrel - and such would clopidogrel not be a more cost effective strategy? In addition, we have existing evidence and experience of prescribing clopidogrel indefinitely for patients who present following a cerebrovascular event - long term safety and efficacy data is available in this context - could this be extrapolated? Should consideration be given to the findigs and outcomes other studies in which the prolonged use of ticagrelor is being	Thank you for your comments. Bleeding events have been added separately to the outcomes listed in the scope. The scope now includes clopidogrel plus aspirin as a comparator. The Committee will consider all available evidence submitted as part of the appraisal process.

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		investigated in the context of ACS e.g. GLOBAL-LEADERS?	

Comment 2: the draft scope

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Background information	AstraZeneca	Please amend the third paragraph to: "After a first myocardial infarction (MI) people remain at significant long-term risk of recurrent atherothrombotic events. Treatment of people who have an MI with oral anti-platelets manages the ongoing risk of having further atherothrombotic events against the increased risk of bleeding associated with this treatment."	Thank you for your comments. The scope has now been updated.
	United Kingdom Clinical Pharmacy Association (UKCPA) Cardiac Group	Not particularly well written - seems to lack depth of information with regards to the actual clinical issue that needs to be addressed. Why is there a clinical need for prolonged high intensity antiplatelet therapy? This hasn't been made clear in the background information.	Thank you for your comment. The background section of the scope provides only a general overview of the disease area. No action required.
The technology/ intervention	AstraZeneca	We suggest re-writing the text to avoid confusion. Ticagrelor (Brilique, AstraZeneca) is an adenosine triphosphate analogue that binds **reversibly** to the P2Y12 class of adenosine diphosphate receptors on platelets and inhibits platelet activation and aggregation. It is administered orally. Ticagrelor co-administered with aspirin, has a marketing authorisation in the UK for "the prevention of atherothrombotic events in adult patients with acute	Thank you for your comment. The technology section has now been updated to clarify the reversibility of the intervention. The section has also been updated to clarify non-

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		coronary syndromes (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction); including patients managed medically, and those who are managed with percutaneous coronary intervention or coronary artery by-pass grafting". Ticagrelor does not currently have a marketing authorisation in the UK for the secondary prevention of atherothrombotic events in people who have had a myocardial infarction **more than 1 year ago**. It has been studied **at 2 doses (60mg and 90mg bid)** in a clinical trial, compared with placebo in adults **aged 50 years or over** who are receiving low dose aspirin and have had a myocardial infarction within 12 to 36 months and have at least 1 of the following risk factors for further atherothrombotic events: age 65 years or more; diabetes mellitus requiring medication; a second prior spontaneous myocardial infarction > 1 year; multi-vessel coronary artery disease; or chronic **non end stage** renal dysfunction.	end stage renal function. The clinical trial section has been updated to clarify that patients in the trial had a myocardial infarction occurring more than 12 months ago however because the background section provides a general overview of the technology, additional details about the clinical trial have not been included.
	United Kingdom Clinical Pharmacy Association (UKCPA) Cardiac Group	No - it should include all P2Y12 inhibitors	Thank you for your comment. NICE can only appraise a technology within its marketing authorisation and therefore prasugrel and clopidogrel cannot be included as interventions for this proposed appraisal. Clopidogrel plus aspirin has been included as a comparator because of

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			its use in clinical practice.
Population	AstraZeneca	Questions for consultation: Has the population been appropriately defined in the scope? The population is defined appropriately. • Are people at an increased risk of atherothrombotic events treated differently in clinical practice depending on how long ago they had their myocardial infarction? With respect to antiplatelet therapies in clinical practice, all patients appear to be treated similarly > 12 months after an MI (i.e. are prescribed aspirin indefinitely), regardless of risk of further atherothrombotic events. • Should the population be stratified depending on how long ago they had their last myocardial infarction? The population may be stratified according to the time since the qualifying MI event.	Comments noted. No action required.
	United Kingdom Clinical Pharmacy Association (UKCPA) Cardiac Group	No - what constitutes a high risk patient?	Thank you for your comment. Stakeholders agreed that the high-risk population is generally defined in line with the trial criteria and this is described in the technology section in the scope

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Comparators	AstraZeneca	Aspirin monotherapy is an appropriate comparator in this setting. However, we believe that since patients intolerant of aspirin are not expected to be eligible to receive ticagrelor, a comparison against clopidogrel monotherapy is not appropriate. Questions for consultation: Have all relevant comparators for ticagrelor been included in the scope? Yes. All relevant comparators have been included. • Is dual antiplatelet therapy with aspirin and other P2Y12 inhibitors (such as clopidogrel or prasugrel) considered for people who have had a prior myocardial infarction at least 12 months ago and are at increased risk of atherothrombotic events? Recent market research with cardiologists, commissioned by AstraZeneca, shows that dual antiplatelet therapy cannot be considered established NHS practice in the population of interest since the second antiplatelet agent (clopidogrel, prasugrel or ticagrelor) is stopped at 12 months after MI. • Which treatments are considered to be established clinical practice in the NHS for secondary prevention of atherothrombotic events after myocardial infarction at least 12 months ago? Further to the previous comment, we understand that current NHS practice for the treatment of patients beyond 12 months from an MI event is for aspirin monotherapy continued indefinitely and that this can be considered 'established clinical practice in the NHS'.	Thank you for your comment. The scope has now been updated to include clopidogrel with aspirin as a relevant comparator. The relevant comparators were discussed at the scoping workshop and the clinical experts agreed that some patients would be eligible for long-term treatment with clopidogrel and aspirin.
	United Kingdom Clinical Pharmacy Association	No - as explained above - the trial is not reflective of UK practice - treatment would not be restarted unless the patient presents with a new index event - the second agent would not be restarted just because the patient is high risk. The decision to continue lifelong/prolonged DAPT is usually made during the	Thank you for your comment. The remit has been updated following positive

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	(UKCPA) Cardiac Group	in-patient stay particularly in those patients who receive several several stents and/or may be at increased risk of stent thrombosis	opinion by the Committee for Medicinal Products for Human Use (CHMP).
Outcomes	AstraZeneca	The outcome measures are broadly appropriate, but we would recommend that the following clarification is made to avoid potential confusion: • Non-fatal myocardial infarction (STEMI and NSTEMI) • Non-fatal stroke	Thank you for your comment. This has now been updated in the scope.
	United Kingdom Clinical Pharmacy Association (UKCPA) Cardiac Group	Yes - ischaemic events, stent thrombosis and bleeding complications are important aspects for consideration.	Thank you for your comment.
Equality and Diversity	United Kingdom Clinical Pharmacy Association (UKCPA) Cardiac Group	The trial itself exludes those patients with a previous stroke, GI bleed or need for anticoagulation - this is not what we do in practice - should these patients present with a further ischaemic event they would still require treatment - the question that would need to be answered is whether long term administration of a p2y12 inhibitor would provide any additional benefits - or would this be offset by the increased bleeding risk?	Thank you for your comments. Bleeding events have now been added to the list of outcomes in the scope.
Innovation	United Kingdom Clinical Pharmacy Association	Yes - technology is innovative Yes - there will be health related benefits - but at what cost?	Comments noted.

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	(UKCPA) Cardiac Group	Consideration should also be given to the outcomes of the DAPT study. There are other studies currently on-going in which long-term treatment with ticagrelor is under investigation e.g. GLOBAL-LEADERS (ACS) - perhaps waiting for the outcomes of this study is warranted to provide further insights into the long-term safety of more potent P2Y12 inhibition.	
Other considerations	AstraZeneca	Questions for consultation: Are the subgroups suggested in 'other considerations appropriate? In the pivotal trial, one of the pre-specified subgroups was "prior revascularisation by PCI". Therefore, please amend the second suggested subgroup to: • People who have or have not had prior revascularisation by percutaneous coronary intervention This is clinically appropriate for the UK, since there is minimal revascularisation by coronary artery bypass graft (CABG) in MI patients. • Should people with a second prior myocardial infarction, multi-vessel coronary artery disease, or with chronic renal dysfunction be examined separately as subgroups? Each of the populations listed were pre-specified subgroups in the pivotal study and could be examined separately as subgroups. • Are there any other subgroups of people in whom ticagrelor is expected to be more clinically effective and cost effective or other groups that should be examined separately? No further subgroups are currently suggested beyond those discussed above.	Thank you for your comment. At the scoping workshop the clinical experts confirmed that people in England can receive revascularisation by coronary artery bypass graft.
	United Kingdom	Should perhaps consider all PY12 inhibitors rather than just ticagrelor	Thank you for your

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	Clinical Pharmacy Association (UKCPA) Cardiac Group		comment. NICE can only appraise a technology within its marketing authorisation and therefore prasugrel and clopidogrel cannot be included as interventions for this proposed appraisal. Clopidogrel plus aspirin has been included as a comparator because of its use in clinical practice.
Additional comments on the draft scope	AstraZeneca	We believe that NICE quality standard 68: Acute coronary syndromes (including myocardial infarction), September 2014, should be included in the list of related NICE recommendations and pathways.	Thank you for your comment this has now been added to the scope.

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

Department of Health
Health Care Improvement Scotland
Royal College of Nursing
Royal College of Pathologists
Thrombosis UK