NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Bayer	Draft recommendation Bayer is pleased with the draft recommendations and agrees that points 1.2 and 1.3 support the most appropriate use of rivaroxaban in this indication: *1.2 Clinicians should carefully assess the person's risk of bleeding before treatment with rivaroxaban is started. The decision to start treatment should be made after an informed discussion between the clinician and the patient about the benefits and risks of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone.* *1.3 Clinicians should reassess the relative benefits and risks of continuing treatment with rivaroxaban, no later than 12 months after starting treatment.* Indeed, Bayer is committed to introducing rivaroxaban 2.5mg as a responsible partner to the NHS, with a focus on the patients with the highest CV risk and lowest risk of bleeding (in line with the European licence). Rivaroxaban 2.5mg will be commercially available in the UK from Friday, 24th October 2014.	Comments noted. At the second Committee meeting it was agreed that 1.3 should be clarified to state that the assessment of risk and benefit should be done regularly (as stated in the summary of product characteristics for rivaroxaban) and the patient should be fully informed of the risks and benefits. 1.3 has been amended to read: A decision on continuation of treatment should be taken no later than 12 months after starting treatment. Clinicians should regularly reassess the relative benefits and risks of continuing treatment with rivaroxaban and discuss them with the patient.

Consultee	Comment	Response
Bayer	Unmet need Bayer is pleased that there is recognition of the remaining *high unmet need* despite current management. Notwithstanding the widespread use of antiplatelet agents in the acute and chronic setting, the incidence of CV events such as CV death or MI in the post-ACS population remains high. Patients who receive recommended dual antiplatelet therapies still have a 10% residual risk of experiencing a major CV event during the 12–15 months after ACS has occurred(1-3). A study in England found that at 7 years, the risk of all-cause mortality in male and female survivors of first acute myocardial infarction was about twice the risk of all-cause mortality in the general population. By 7 years, the risk of all-cause mortality in both male and female survivors of recurrent AMI was about 3 times higher than the risk of dying in the general population(4).	Comments noted. No changes to document needed.

Consultee	Comment	Response
Bayer	Innovative approach Bayer is also pleased to note that the clinical experts advising the appraisal committee observed that due of its different mechanism of action, rivaroxaban could be a useful additional treatment option for some patients receiving clopidogrel plus aspirin or aspirin alone. The central role of thrombosis in the pathophysiology of ACS, and the platelet-rich composition of arterial thrombi, provide a rationale for the use of antiplatelet agents. After the rupture or erosion of an atherosclerotic plaque, platelets are recruited to the plaque where they adhere to the vessel wall and recruit further platelets, leading to rapid growth of the thrombus. After atherosclerotic plaque rupture in patients with ACS, the presence of tissue factor in atherosclerotic plaques and in the blood (following endothelial damage), alongside activated platelets, triggers the coagulation cascade, leading to the generation of thrombin and the conversion of fibrinogen to fibrin, which stabilizes the ACS clot(5-10). In parallel, thrombin stimulates platelets by binding to protease-activated receptor 1 (PAR1; also known as the thrombin receptor), inducing release of adenosine diphosphate and thromboxane A2, which further stimulates platelet activation and aggregation(11;12). Most thrombin is produced on the platelet surface, and binding of thrombin to platelets via glycoprotein Ibα is believed to contribute to platelet activation(13). Because of these various interactions, mechanisms of platelet activation and coagulation are highly interdependent, with thrombin playing a central role in both.	Comments noted. No changes to the document needed.

Consultee	Comment	Response
Bayer	Innovative approach continued Anticoagulants are an important component of therapy for ACS in the acute setting. However, excess thrombin generation has been found to persist in stable patients for at least 6–12 months beyond the acute presentation of ACS(14;15), providing a rationale for long-term oral anticoagulant therapy for the prevention of recurrent events. The use of anticoagulant therapy in combination with antiplatelet therapy targets complementary mechanisms associated with thrombus formation in patients with ACS. Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban is a significant advance in the secondary prevention of ACS in patients with elevated biomarkers. The *dual pathway treatment strategy*, which recognises the importance of thrombin generation following ACS events and the role that rivaroxaban can play in this, on top of dual antiplatelet therapy offers an *innovative approach* to prevent atherothrombotic events and provides significant mortality benefit. Of note *rivaroxaban is the only novel OAC with this indication.*	Comments noted. No changes to the document needed.

Consultee	Comment	Response
Bayer	Mortality benefit and safety Bayer is pleased to note that the Committee recognised the positive risk benefit profile of rivaroxaban for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. The ATLAS ACS 2 TIMI 51 trial(16) demonstrated that the theoretical benefit of adding an oral anticoagulant (rivaroxaban) to the treatment pathway is translated into improved clinical outcomes. The 2.5mg rivaroxaban dose was superior to placebo for the primary efficacy endpoint (Composite of death from CV causes, myocardial infarction, and stroke): 6.2% vs. 7.9%; HR=0.80; 95% CI 0.68-0.94; p=0.007) The event rate for the individual component of CV death was 1.7% in the rivaroxaban 2.5 mg bd group compared to 3.1% in the placebo group with a HR for CV death of 0.55 (95% CI 0.41-0.74) and a p-value of <0.001. The overall incidence of treatment-emergent non-CABG TIMI major bleeding events, the principal safety outcome, was low. Rivaroxaban 2.5mg twice daily as compared with placebo increased the rates of non-CABG TIMI major bleeding (1.3% vs 0.4%; HR 3.44; 95% CI 1.97-6.01 p<0.001) without an increase in fatal bleeding (0.1% vs 0.2%; HR 0.38 95% CI 0.1-1.45; p=NS). On balance, the increase in bleeding risk is outweighed by the substantial reduction in risk of death, particularly CV death, from which patients are at high risk after diagnosis of ACS. The benefit risk was further improved in the licensed population (compared to the overall trial population) because of the increased numbers of ischaemic events prevented.	Comment noted. The data presented is in the company submission and has as such already been considered by the Committee.

Consultee	Comment	Response
Bayer	Cost-effectiveness Bayer is pleased to note that despite difference in opinion in the modelling methodology, the ICERs presented by both Bayer and the ERG were all lower than £10,000 per QALY gained. This led the appraisal committee to conclude that *'Rivaroxaban can be considered a cost-effective use of NHS resources.'* Reference list not published here.	Comment noted. No changes to the document needed.

Comments received from clinical experts and patient experts

Nominating organisation	Comment	Response
Company's nominated clinical expert	Few comments: 1. in 2.1 at the end you mention ticlopidine which is in practice not available in the UK and was not truly studied in combination with rivaroxaban (if I understand well used in less than 1% of the patients recruited in ATLAS). I suggest deleting this point. 2. I think a further point should be added to the recommendations stating that **"Rivaroxaban has not been studied in combination with the newer antiplatelet agents Prasugrel and Ticagrelor. Recommendations for use of these agents have been addressed in previous NICE documents –quote NICE appraisal 236 etc-. At present the combined use of rivaroxibam with Prasugrel and Ticagrelor is not recommended."** **3.** in 3.10 you state" vital status was unknown for 1117 (86.3%) patients". It is obviously the other way around (13.7%)	Comment noted. The wording in 2.1 reflects the European marketing authorisation of vedolizumab. Section 2.1 has been updated to state that ticlopidine is not listed in the British National Formulary (BNF). The recommendations state that rivaroxaban is recommended in combination with aspirin plus clopidogrel or aspirin alone. NICE can only make recommendations within a technology's marketing authorisation. The summary of product characteristics for rivaroxaban states that the efficacy and safety of rivaroxaban has been investigated in combination with the antiplatelet agents aspirin and clopidogrel/ ticlopidine. Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended. The statement in 3.10: At the end of the trial, of the 1294 patients who withdrew consent, vital status was unknown for 1117 (86.3%) patients reflects the data presented in the company's submission.

Comments received from commentators

Commentator	Comment	Response
Royal College of Nurses	No comments	Noted.
Department of Health	No comments	Noted.

Comments received from members of the public

Role*	Section	Comment	Response
Healthcare industry	general	AstraZeneca UK Ltd would like to thank NICE for providing the opportunity to comment on the technology appraisal for rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome.	Comment noted.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
(pharmaceutical)	1.1	Given UK clinical practice and NICE guidelines, AstraZeneca firmly believes that the recommendation for rivaroxaban in combination with aspirin (alone) should be restricted to those patients who cannot take a second antiplatelet (ticagrelor, clopidogrel or prasugrel). In UK practice, the patients who receive aspirin without a second antiplatelet are those with lowest CV risk or those who cannot take a second antiplatelet. The NICE guideline – Early management of unstable angina and NSTEMI (CG94) recommends that dual antiplatelet therapy be prescribed to all post-MI patients bar those with the 'lowest' CV risk[1]. In these patients of lowest CV risk, the benefits of prescribing a second antiplatelet are not deemed to outweigh the risks (of bleeding). As such, if a clinician has determined that the prescribing of a second antiplatelet is not justified, it would not be logical that the prescribing of rivaroxaban would be, given the bleeding risk carried by rivaroxaban. As such the recommendation for rivaroxaban in combination with aspirin (alone) should be restricted to those patients who cannot take a second antiplatelet. Suggested wording for recommendation 1.1: "Rivaroxaban is recommended as an option, in combination with aspirin plus clopidogrel, or in combination with aspirin alone when the patient cannot take a second antiplatelet, for preventing atherothrombotic events in people who have had an acute coronary syndrome with elevated cardiac biomarkers" [1] National Institute for Health and Care Excellence. Clinical guideline CG94 - The early management of unstable angina and non-ST-segment-elevation myocardial infarction	Comments noted. Rivaroxaban was found to be cost effective in the whole population for whom it is indicated and as such was recommended as an option for the whole population covered by the marketing authorisation.

Role*	Section	Comment	Response
	1.2	AstraZeneca believes that the recommendation for rivaroxaban after acute management of ACS should be restricted to specialist initiation only, since specialists are best placed to assess the balance of risks and benefits associated with initiation. According to the Summary of Product Characteristics (SmPC), rivaroxaban should only be initiated in patients with elevated cardiac biomarkers, who have been stabilised, with no previous TIA/stroke. Further, rivaroxaban should be prescribed with caution in patients aged under 75 years and in patients who weigh <60Kg[2]. It is the specialist in the acute setting (post stabilisation) who is best positioned to have all the necessary information at their disposal upon which to base the prescribing decision. The SmPC also states that rivaroxaban should be commenced as soon as possible after stabilisation. In UK clinical practice, patients are typically discharged from hospital with 4 weeks drug therapy following an ACS event, meaning these patients do not come into contact with their GP for this period of time [2] Xarelto 2.5mg Summary of Product Characteristics <https://www.medicines.org.uk> (accessed November 2014)	Comments noted. Section 4.2 has been updated to read: The Committee heard from its GP members that, after an acute coronary syndrome event, patients would usually be seen by their GP within 1 week of being discharged from hospital. The Committee considered that a discharge summary which is sent to the patient's GP at the time of discharge would give sufficient information for the GP to start treatment with rivaroxaban.
	1.3	AstraZeneca suggests that the wording of recommendation 1.3 "Clinicians should reassess the relative benefits and risks of continuing treatment with rivaroxaban, no later than 12 months after starting treatment" be amended to reflect the wording used at section 2.2 "Treatment with rivaroxaban should be regularly evaluated in the individual patient, weighing the risk of ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis because experience up to 24 months is limited" which reflects section 4.2 of the SmPC[2]	Comments noted. At the second Committee meeting it was agreed that 1.3 should be clarified to state that the assessment of risk and benefit should be done regularly (as stated in the summary of product characteristics for rivaroxaban) and the patient should be fully informed of the risks and benefits. 1.3 has been amended to read: A decision on continuation of treatment should be taken no later than 12 months after starting treatment. Clinicians should regularly reassess the relative benefits and risks of continuing treatment with rivaroxaban and discuss them with the patient.