Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Rivaroxaban for the treatment of acute coronary syndrome

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment of acute coronary syndrome.

Background

The term acute coronary syndrome (ACS) is used to refer to a group of clinical symptoms associated with acute myocardial ischaemia. It encompasses a spectrum of disorders including acute myocardial infarction (MI) and unstable angina pectoris. ACS is usually the result of an acute or sub-acute primary reduction of myocardial oxygen supply provoked by disruption of an atherosclerotic plaque (build-up of material within heart vessel) associated with inflammation, thrombosis, vasoconstriction and microembolisation. In 2009/10 there were 40,000 hospital admissions for unstable angina, and 57,000 admissions for acute MI with 28,000 subsequent MIs in England. ACS becomes more prevalent with increasing age and incidence is higher in men than women.

The presence of persistent ST-segment-elevation on an electrocardiogram usually indicates total occlusion of the affected artery, resulting in necrosis of the tissue supplied by that artery (acute MI). This condition (STEMI) is treated immediately with reperfusion therapy (thrombolysis or percutaneous coronary intervention [PCI]). ACS without ST-segment-elevation is classified as either unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI). NSTEMI differs from unstable angina primarily in the severity of myocardial ischaemia. In NSTEMI, the ischaemia is severe enough to result in the release of biochemical markers of myocardial injury into the blood. Immediate treatment for these conditions aims to prevent progression to total occlusion of the artery and, for people at high risk of MI, may include coronary revascularisation, either by means of PCI or coronary artery bypass graft.

Long term management of ACS includes the use of aspirin and clopidogrel. In addition, a glycoprotein IIb/IIIa inhibitor (abciximab; eptifibatide; tirofiban) may be used. Other possible treatments include anticoagulants (heparin and low-molecular-weight heparin), vasodilators (nitrates), calcium channel blockers and beta-blockers.

In NICE Technology Appraisal no. 203, bivalirudin is recommended in combination with aspirin and clopidogrel for the treatment of ST-segment-elevation myocardial infarction in people undergoing percutaneous coronary

intervention. Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention, only when: immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary; stent thrombosis has occurred during clopidogrel treatment or the patient has diabetes mellitus (NICE Technology Appraisal No. 182). NICE has also produced clinical guidelines on secondary prevention in primary and secondary care for patients following a MI (Clinical Guideline No. 48) and the early management of unstable angina and non-ST-segment-elevation myocardial infarction (Clinical Guideline No. 94). According to these guidelines, it is recommended that clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of non-ST-segment-elevation ACS. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended. Glycoprotein IIb/IIIa inhibitors are also recommended as part of the early management for patients who have an intermediate or higher risk of adverse cardiovascular events.

The technology

Rivaroxaban (Xarelto, Bayer) is a highly selective direct factor Xa inhibitor anticoagulant which acts by direct inhibition of activated factor X (factor Xa). Factor Xa is a key component in the formation of blood clots. It is administered orally.

Rivaroxaban does not hold a UK marketing authorisation for the treatment of acute coronary syndrome. It is being studied in a placebo-controlled clinical trial for people hospitalised for acute coronary syndrome (STEMI, NSTEMI and unstable angina) who are receiving either aspirin alone or dual-antiplatelet therapy with aspirin and a thienopyridine (clopideogrel or ticlopidine).

Intervention(s)	Rivaroxaban in combination with aspirin or with aspirin and a thienopyridine
Population(s)	Adults hospitalised for acute coronary syndrome (STEMI, NSTEMI, unstable angina)

Comparators	For people who are to be managed with PCI: • bivalirudin in combination with aspirin and clopidogrel • prasugrel in combination with aspirin • ticagrelor in combination with aspirin (subject to ongoing NICE technology appraisal) For people who are not to be managed with PCI: • clopidogrel in combination with aspirin • ticagrelor in combination with aspirin (subject to ongoing NICE technology appraisal)
Outcomes	The outcome measures to be considered include: • mortality • thrombotic cardiovascular events • need for revascularisation • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows the following subgroups will be considered: people with unstable angina, NSTEMI, and STEMI. Guidance will only be issued in accordance with the marketing authorisation.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No.182, October 2009, 'Prasugrel for the treatment acute coronary artery syndromes with percutaneous coronary intervention'. Review Date January 2012 Technology Appraisal No. 230, July 2011, 'Bivalirudin for the treatment of ST-segment elevation myocardial infarction (STEMI)'. Review Date July 2014 Technology Appraisal in Preparation, 'Ticagrelor for the treatment of acute coronary syndromes (ACS)'. Earliest anticipated date of publication October 2011 Related Guidelines: Clinical Guideline No. 48, May 2007, 'Secondary prevention in primary and secondary care for patients following a myocardial infarction'. Under review. Clinical Guideline No. 94, March 2010, 'Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction'. Review Date March 2013.

Questions for consultation

Have the most appropriate comparators for rivaroxaban for the treatment of acute coronary syndrome been included in the scope?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Please consider whether in the remit or the scope there are any issues relevant to equality. Please pay particular attention to whether changes need to be made to the remit or scope in order to promote equality, eliminate unlawful discrimination, or foster good relations between people who share a characteristic protected by the equalities legislation and those who do not share it, or if there is information that could be collected during the assessment process which would enable NICE to take account of equalities issues when developing guidance.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be

included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)