Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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rivaroxaban 2.5mg film-coated tablets (Xarelto®) SMC No. (1062/15)

Bayer plc.

05 June 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

rivaroxaban (Xarelto®) is not recommended for use within NHS Scotland.

Indication under review: rivaroxaban co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

Rivaroxaban in addition to standard care significantly reduced the occurrence of the primary composite endpoint: death from cardiovascular causes, myocardial infarction, or stroke, compared to standard care alone.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Rivaroxaban co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

Dosing Information

The recommended dose is rivaroxaban orally 2.5mg twice daily.

Patients should also take a daily dose of 75mg to 100mg aspirin or a daily dose of 75mg to 100mg aspirin in addition to either a daily dose of 75mg clopidogrel or a standard daily dose of ticlopidine.

Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited.

Treatment with rivaroxaban should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.

Product availability date

October 2014.

Summary of evidence on comparative efficacy

Rivaroxaban is a highly selective direct factor Xa inhibitor, and treatment results in interruption of the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and has no effects on platelets.[1] Rivaroxaban is the first anticoagulant to gain marketing authorisation for use with aspirin ± clopidogrel for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers. Current Scottish guidance in patients with ACS includes the use of long term aspirin therapy in addition to clopidogrel for one to 12 months although these recommendations are currently being updated.[2] Some clinical experts consulted by SMC have reported the use of aspirin plus ticagrelor as first line treatment.

ATLAS-ACS 2 TIMI 51 was a phase III randomised placebo-controlled study to evaluate the efficacy and safety of rivaroxaban in addition to anti-platelet therapy in 15,526 patients with ACS.[3-5] Patients aged ≥18 years were recruited to the study if they presented with symptoms suggestive of an ACS and in whom an ST segment elevation myocardial infarction (MI) (STEMI), a non-ST-segment elevation MI (NSTEMI), or unstable angina had been diagnosed. Patients <55 years of age had either diabetes mellitus or a previous MI in addition to the index event.[3] Patients with a STEMI had to have elevation of biomarkers of myocardial necrosis (CK-MB or troponin).[4]

Patients were randomised, stratified on the basis of planned use of a thienopyridine, to oral treatment with rivaroxaban 2.5mg twice daily (licensed dose), rivaroxaban 5mg twice daily, or placebo in addition to standard medical therapy (including low-dose aspirin ± a thienopyridine [clopidogrel or ticlopidine] according to the national or local guidelines). The majority of patients (n=14,473) were in stratum 2 (aspirin + thienopyridine). The study was event driven with >75% exposed to treatment for ≥6 months;

the mean duration of treatment with study drug was 13.1 months and with a thienopyridine was 13.3 months.[3-5]

The primary efficacy endpoint was a composite endpoint: first occurrence of MI, stroke (ischaemic, haemorrhagic, or stroke of uncertain cause), or death from cardiovascular (CV) causes, adjudicated by a clinical events committee who were unaware of the study group assignments. The modified intention-to-treat (mITT) population was used for efficacy analyses. The primary endpoint occurred in 6.1% (626/10,229) versus 7.4% (376/5,113) of patients in the rivaroxaban (combined doses) and placebo groups respectively; hazard ratio, 0.84; 95% confidence interval (CI): 0.74 to 0.96; p=0.008. This was primarily driven by CV deaths. Using a closed hierarchical testing procedure, a comparison of each dose of rivaroxaban with placebo was allowed for the primary and then secondary endpoints until no significant difference was found at which point statistical testing was halted. The primary safety endpoint was major bleeding associated with thrombolysis in MI (TIMI) not related to coronary-artery bypass grafting (CABG) and was significantly higher for rivaroxaban than placebo-treated patients. Primary (efficacy and safety) and secondary efficacy endpoints for the licensed dose of rivaroxaban versus placebo are included in the table below.[3-5]

Table; primary (efficacy and safety) and some secondary endpoints (mITT population, licensed dose) [3,4]

	Rivaroxaban 2.5mg twice daily	**Placebo**	**HR (95% CI), p-value**
Primary efficacy endpoint			
N; number of patients (mITT)	5,114	5,113	
CV death, MI, or stroke; % (n/N)	6.1% (313/5,114)	7.4% (376/5,113)	0.84 (0.72 to 0.97), p=0.02
Components of primary endpoint*			
CV death; %	1.8%	2.8%	0.66 (0.51 to 0.86), p=0.002
MI; %	4.0%	4.5%	0.90 (0.75 to 1.09), p=0.270
Stroke; %	0.9%	0.8%	1.13 (0.74 to 1.73), p=0.562
Secondary endpoints			
Secondary endpoint 1: death from any cause, MI, or stroke; % (n/N)	6.3% (320/5,114)	7.5% (386/5,113)	0.83 (0.72 to 0.97), p=0.016
Secondary endpoint 2: Net clinical outcome; % (n/N)	7.1% (361/5,114)	7.6% (391/5,113)	0.93 (0.81 to 1.07), p=0.320
Primary safety endpoint			
N; number of patients (safety)	5,115	5,125	
TIMI major bleeding not related to CABG; % (n/N)	1.3% (65/5,115)	0.4% (19/5,125)	3.46 (2.08 to 5.77), p<0.001

HR=hazard ratio, CI=confidence interval, MI=myocardial infarction, CV=cardiovascular, CABG=coronary-artery bypass grafting, TIMI=thrombosis in MI. Net clinical outcome was defined as CV death, MI, ischemic stroke, or non-CABG TIMI major bleeding. *patients could have ≥1 component event.

A post hoc analysis in the population applicable to the licensed indication (biomarker positive excluding prior stroke and transient ischaemic attack patients) was undertaken and included 4,104 patients in the rivaroxaban 2.5mg twice daily group and 4,160 patients in the placebo group. The proportion of patients who met the primary efficacy endpoint was 6.2% versus 7.9% in the rivaroxaban 2.5mg twice daily and placebo groups respectively; hazard ratio 0.80 (95% CI: 0.68 to 0.94), p=0.007. The proportion of patients who met the secondary endpoint of death from any cause, MI, or stroke was 6.4% versus 8.1% respectively; hazard ratio 0.80 (95% CI: 0.68 to 0.94), p=0.007. The primary safety

endpoint occurred in 1.3% versus 0.4% respectively; hazard ratio 3.44 (95% CI: 1.97 to 6.01), p<0.001.[4]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The proportion of patients with a treatment-emergent adverse event was 54% in the rivaroxaban 2.5mg twice daily group versus 53% in the placebo group. Treatment emergent adverse events that led to permanent discontinuation of study drug occurred in 8.7% versus 7.6% of patients in the rivaroxaban 2.5mg twice daily and placebo groups, respectively. Treatment-emergent serious adverse events occurred in a similar proportion of patients (20%) in the rivaroxaban 2.5mg twice daily and placebo groups.[4]

In the rivaroxaban 2.5mg twice daily and placebo groups the proportion of patients with: TIMI minor bleeding were 0.6% and 0.4%, TIMI bleeding requiring medical attention were 9.6% and 5.5% and intracranial haemorrhage were 0.3% and 0.1%, respectively.[4]

Adverse events not related to bleeding were reported in a similar proportion of patients in all groups and included (in the rivaroxaban 2.5mg twice daily and placebo groups respectively): atrial fibrillation (1.2% versus 1.3%), cardiac failure (2.2% versus 1.8%), cough (1.2% versus 1.4%), dyspnoea (1.1% versus 1.5%), chest pain (2.2% versus 1.8%), non-cardiac chest pain (1.7% versus 1.9%), hypertension (1.7% versus 1.5%), nasopharyngitis (0.9% versus 1.0%), increase in alanine aminotransferase (0.9% versus 1.0%) and dizziness (1.2% versus 1.0%).[3]

Summary of clinical effectiveness issues

Rivaroxaban is the first anticoagulant to gain marketing authorisation for use with aspirin alone or in addition to clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers. Current Scottish guidance in patients with ACS is the use of long term aspirin therapy in addition to clopidogrel for one to 12 months although these recommendations are currently being updated. Other licensed treatments include ticagrelor or prasugrel, both used in combination with aspirin. Some clinical experts consulted by SMC have reported that local treatment guidelines for pharmacological management of ACS currently advocate use of aspirin plus ticagrelor as first line treatment option.

In the pivotal study (ATLAS-ACS 2 TIMI 51), treatment with rivaroxaban significantly reduced the composite primary efficacy endpoint of CV deaths, MI and stroke by 16% compared with placebo in patients who were receiving concomitant aspirin ± clopidogrel or ticlopidine. The absolute difference was 1.3%. This was largely driven by the reduction in CV deaths, including a reduction in fatal MIs. The benefit of rivaroxaban was consistently demonstrated irrespective of whether the event that led to study recruitment was STEMI, NSTEMI or unstable angina. However, the study population may not be representative of general population with ACS due to study patients being younger and with less co-morbidity. Nevertheless, the European Medicines Agency (EMA) noted that the study population was similar to other recent clinical studies of ACS. The mean duration of treatment with the thienopyridine was 13.3 months. This is longer than current Scottish guidance, although this is currently being updated. The proportion of patients who had undergone a PCI was low in the study (60%) and results were less impressive in this patient group.[4] The licensed indication does not include a claim for a reduction of stent thrombosis.[1]

Another limitation of the study was the high proportion of patients who prematurely discontinued from the study. However, demographic and disease characteristics in patients that discontinued were compared with the overall study population and found to be more similar to the patients that survived than to those that died, which provided some reassurance.[4] Compared with placebo, rivaroxaban 2.5mg twice daily had no statistically significant effect for the secondary endpoint of net clinical outcome defined as CV death, MI, ischemic stroke, or non-CABG TIMI major bleeding. However, some events were included in the efficacy and safety components of the net clinical outcome which resulted in double counting. Due to the hierarchical testing procedure statistical analyses of remaining secondary outcomes were not performed.

A post hoc subgroup analysis provides efficacy data for the patients eligible for treatment within the licensed indication. The incidence, severity, management and outcome of bleeding events in the licensed population and particularly in patients at increased risk of bleeding is to be assessed through a post authorisation study programme.

TIMI major bleeding not related to CABG was significantly higher in rivaroxaban than placebo treated patients as was TIMI bleeding requiring medical attention. While the EMA considered that the bleeding risk was manageable in the study population, they noted that there were a small number of patients at a higher risk of bleeding and the impact and management of bleeding in these patients is unknown.[4] The summary of product characteristics notes that treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks.[1]

Prescription cost analysis data from NHS National Services Scotland for 2013/14 in primary care indicate use of clopidogrel and some use of ticagrelor [7] In addition, some clinical experts consulted by SMC confirmed the use of aspirin plus ticagrelor as first-line treatment. No comparative efficacy data for rivaroxaban + aspirin + clopidogrel versus this treatment strategy were presented in the company's submission. At the request of SMC, a Bucher adjusted indirect comparison was provided by the submitting company to compare aspirin + clopidogrel + rivaroxaban with aspirin + ticagrelor using the common comparator arm of aspirin + clopidogrel. Two efficacy outcomes (mortality and non-fatal events) and a safety outcome (non-CABG related TIMI major bleed) were analysed. There were no significant differences between treatments for the efficacy outcomes, but non-CABG related TIMI major bleed was significantly lower for aspirin + ticagrelor than aspirin + clopidogrel + rivaroxaban. Limitations of the indirect comparison included heterogeneity in study populations and differences in the results of outcomes for the aspirin + clopidogrel arms, particularly for the safety outcome. The results of the indirect comparison should be interpreted with caution.

Rivaroxaban in combination with prasugrel or ticagrelor has not been studied and is not recommended.[1]

The dose of rivaroxaban for the indication under review is lower than the doses used for the indications of: treatment and prevention of recurrent deep vein thrombosis and pulmonary embolism' prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery' and prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation.[8,9]

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing rivaroxaban in addition to standard care, with standard care alone, in adult patients after an ACS with elevated cardiac biomarkers. Standard care consisted of aspirin with or without clopidogrel. The comparator was selected on the basis that these are the predominant treatments for these patients in Scotland.

A Markov cohort model was used which consisted of an observation period and an extrapolation period. The base case analysis used a lifetime (40 years) time horizon. The observation period was 2 years with model cycles lasting 12 weeks to reflect the clinical data. In the extrapolation period, outcomes were extrapolated using a combination of published data and assumptions. The Markov model included 16 health states to capture ACS events, such as MI, stroke, and intracranial haemorrhage. The model allowed patients to experience up to 3 events and also included other CV deaths and non-CV deaths. Other features in the model included transient health states to capture adverse events (primarily bleeding) and revascularisations (PCI and CABG). The model also accounted for different costs and utilities depending on the time since the event through the use of tunnel states.

The source of clinical data for the observation period was the ATLAS-ACS 2 TIMI 51 study. Patient level data from the licensed population post-hoc subgroup analysis were used to derive transition probabilities for the observation period of the model. However, instead of using the study data directly in the model, the event rate data were modelled using a Weibull function. The company justified this approach as there were challenges with deriving the transition probabilities directly from the clinical data due to fewer observations in the later cycles. In order to account for patients stopping clopidogrel treatment after 1 year, the transition probabilities in both arms were adjusted based on data from a separate clopidogrel study. An additional adjustment was made to the efficacy data and the discontinuation rates on the basis that clinical opinion indicated most patients would be likely to discontinue treatment with rivaroxaban in the second year. In the study, around 70% of patients continued treatment in year 2, but the clinical data used in the model were adjusted to reflect only 19% of patients continuing treatment in year 2.

In the extrapolation period, a combination of published literature, clinical opinion and assumptions were used to derive the transition probabilities. A key assumption in the model is that there is no additional treatment effect associated with rivaroxaban or clopidogrel beyond the treatment period. The same transition probabilities were applied in each arm of the model in the extrapolation period. In general, the transition probabilities from the last 12-week cycle of the observation period from the comparator arm were used as all patients would be treated with aspirin monotherapy beyond year 2. For patients who experienced an event, the relative risks of subsequent events were estimated based on data from the pivotal study (showing a decrease in the number of events over time) and published estimates showing patients who experience an event continue to have a higher risk of subsequent events (assumed to be 1.5 times higher than the general population). The transition probabilities over the longer-term were adjusted for age, with age-specific increases in the risk of experiencing MI and strokes estimated using UK age-specific incidence rates from published studies.

Quality of life data were collected in the study using EQ-5D but the company did not use these data to derive utility values due to the study not being powered to detect differences in quality of life. However, a sensitivity analysis was provided which used these data. In the base case analysis, utility data from published UK studies were used instead. The utility value for the no event health state was 0.842 and for the acute phase (first 6 months) following an MI or stroke the values used were 0.779 and 0.703 respectively. For multiple events, the utility values of the relevant event were multiplied together e.g. if a patient suffered an MI followed by another MI the utility value applied to this health state would be 0.607. The utility values were also age-adjusted to reflect the age of patients over the model time horizon. For bleeding events, the utility values used in the model were 0.75 and 0.8 for major and minor bleeds respectively. Major bleeds were assumed to impact quality of life for 30 days, whereas the effect of other bleeds only lasted 2 days.

The analysis included the medicine costs for rivaroxaban, clopidogrel and aspirin. As all treatments are oral, no administration costs were included. The costs of bleeds were included according to severity. In the base case, patients were assumed to be treated with rivaroxaban 2.5mg for 2 years

and clopidogrel treatment was assumed to be for 1 year. While the duration of clopidogrel treatment may not be appropriate for all patients, it will not result in a bias as it is included in both arms of the model. Resource use included health state costs (MI and stroke) and revascularisation procedures. The acute event costs were based on NHS reference costs plus some assumptions were made to estimate ongoing treatment costs following the initial event. These ongoing costs were applied for the model duration.

In the base case analysis, the submitting company estimated a cost per quality-adjusted (QALY) of £7,756 based on an incremental cost of £822 and a QALY gain of 0.11. The key driver of the incremental cost was the drug cost of rivaroxaban with some cost offsets due to a reduction in MIs and deaths.

A range of sensitivity analyses were conducted which showed the key drivers of the results were the cost of rivaroxaban, the discount rate, the direct costs of an MI, and the utility value applied to the no event health state. The incremental cost-effectiveness ratio (ICER) remained below £10k per QALY in all scenarios, except when the time horizon was reduced to 5 years resulting in an ICER of £18k per QALY. An analysis based only on the observation period (i.e. 2 years) was also provided which resulted in an ICER of £44k per QALY.

The following limitations were noted:

- The comparator used in the analysis may not be appropriate. While aspirin plus clopidogrel is used in practice, SMC clinical experts confirmed aspirin plus ticagrelor is also used. An economic analysis versus aspirin plus ticagrelor was provided by the submitting company which resulted in an ICER of £11k per QALY based on an incremental cost of £720 and a QALY gain of 0.07. However, this analysis was based on non-significant differences in efficacy from the indirect comparison. An additional analysis was provided which removed the non-significant differences and this showed the treatments had similar efficacy, but aspirin plus ticagrelor was associated with a significantly lower risk of major bleeds. Therefore, rivaroxaban was dominated by ticagrelor as it was estimated to result in an incremental cost of £105 and a small QALY loss of 0.0001. While the Committee acknowledged there are limitations with the indirect comparison which underpins this analysis, the comparison with ticagrelor was considered to be relevant.

- No costs were included in the no event health state of the model. It seems unlikely that these patients would not incur any additional resource, particularly as all patients who enter the model have previously experienced a CV event. This would bias the results in favour of rivaroxaban as more patients remain in the no event health state. Sensitivity analysis was subsequently provided which included a cost of £2k per year in this health state. This resulted in an ICER of £11k per QALY for the analysis versus aspirin plus clopidogrel.

- The stroke and major bleed utility values used in the model seem too high and as a result may not fully capture quality of life loss associated with these events. Sensitivity analysis was provided using lower utility values and this showed the results were not overly sensitive to changes in these parameters. A scenario analysis was also provided to test the base case comparison versus aspirin plus clopidogrel which used a 1-year treatment duration, lower utility values for stroke and major bleed, a cost of £5k per year for the no event health state, and reduced the time horizon to 10 years. This resulted in an ICER of £14k per QALY.

Due to the issues outlined above, particularly the results of the additional analysis versus aspirin plus ticagrelor, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

Scottish Intercollegiate Guidelines Network (SIGN) guideline 93; Acute coronary syndromes was updated in February 2013.[2] Based on the highest level of evidence, aspirin (300mg) should be immediately given to patients with an acute coronary syndrome (ACS). Both aspirin (300mg) and clopidogrel (300mg) should be immediately given if there are ischaemic electrocardiographic changes or elevated cardiac markers. All patients with ACS should be maintained on long-term aspirin therapy (75 to 150mg/day), and in addition clopidogrel should be continued for three months in patients with non-ST elevation ACS, or for up to four weeks in patients with ST elevation ACS.

National Institute for Health and Care Excellence (NICE) has published three clinical guidelines (CG) relevant to the indication under review: CG94 Unstable angina and NSTEMI was published in 2010; CG167 MI with ST segment elevation and CG172 MI secondary prevention were published in 2013.[10-12]

CG172 recommends aspirin should be offered to all patients after an MI and continued indefinitely, unless the patient cannot tolerate aspirin or anticoagulation is indicated. In addition to low-dose aspirin, ticagrelor is recommended for up to 12 months as a treatment option in adults with ACS. Clopidogrel is a recommended treatment option for up to 12 months in patients who have had an NSTEMI, regardless of treatment, or who have had a STEMI and received a bare-metal or drug-eluting stent. In patients who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent, clopidogrel is a treatment option for at least 1 month and up to 12 months. The second antiplatelet agent should be continued for up to 12 months in people who have had a STEMI and who received coronary artery bypass graft surgery. The guideline recommends that a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) should not be added in combination with dual antiplatelet therapy in patients who otherwise need anticoagulation, who have had an MI. In patients who have had an MI and otherwise need anticoagulation warfarin should be considered, and treatment with a new oral anticoagulant should be discontinued unless there is a specific clinical indication to continue it.[12]

The European Society of Cardiology (ESC) has published three guidelines relevant to this indication.[13-15]

In 2014, ESC updated the guideline on myocardial revascularisation which states “the role of direct acting oral anticoagulants in combination with dual anti-platelet therapy in secondary prevention of ACS is promising, but the interpretation of the totality of evidence for the class of oral anticoagulants is inconclusive and requires further study”.[13]

The ESC guidelines for the management of acute MI in patients presenting with ST-segment elevation (2012) advise, based on low-level evidence (data derived from a single randomised clinical trial), that low-dose rivaroxaban (2.5 mg twice daily) may be considered in selected patients who receive aspirin and clopidogrel if the patient is at low bleeding risk.[14]

The ESC guidelines on non-ST segment elevation ACS (2011) recommend all patients without contraindications should be given a loading dose of aspirin (150 to 300mg), and a maintenance dose of 75 to 100mg daily long-term regardless of treatment strategy. A P2Y12 inhibitor (clopidogrel,

prasugrel, ticagrelor) should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.[15]

Additional information: comparators

Aspirin ± clopidogrel, ticagrelor (+ aspirin), prasugrel (+ aspirin).

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
rivaroxaban*	**2.5mg orally twice daily**	**764**
ticagrelor¥	90mg orally twice daily	712
prasugrel¥	10mg orally once daily (follow loading dose of 60mg)	627
clopidogrel¥	75mg orally once daily	24
Aspirin	75mg orally once daily	11

Costs from eVadis (March 2015). *administered with aspirin ± clopidogrel. ¥administered with aspirin.

Additional information: budget impact

The company estimated there would be 7,499 patients eligible for treatment in year 1, rising to 7,620 patients in year 5, with an estimated market share of 5% (375 patients) in year 1 and 14% (1,067 patients) in year 5. A discontinuation rate was also included each year to account for patients being at different stages of their treatment.

The gross medicines budget impact was estimated to be £296k in year 1, rising to £842k in year 5. There were no displaced medicines included on the basis that rivaroxaban would be used in addition to standard care, which the company assumed is clopidogrel plus aspirin. As such, the net medicines budget impact was as per the gross impact estimates.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Bayer plc. Summary of product characteristics for rivaroxaban (Xarelto®) 2.5mg film-coated tablets. Last updated December 2014

2. Scottish Intercollegiate Guidelines Network. SIGN 93: Acute coronary syndromes. A National clinical guideline. Updated February 2013. Healthcare Improvement Scotland; 2013.

3. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome (including supplementary appendices). New Engl J Med 2012;366(1):9-19.

4. European Medicines Agency. Xarelto Assessment Report (EPAR). 2013. Report No.: EMA/CHMP/794349/2012.

5. *Commercial In Confidence*

6. *Commercial In Confidence.*

7. NHS NSS. ISD; Prescription Cost Analysis for financial year 2013/14. May 2014.

8. Bayer plc. Summary of product characteristics for rivaroxaban (Xarelto®) 10mg film-coated tablets. Last updated December 2014

9. Bayer plc. Summary of product characteristics for rivaroxaban (Xarelto®) 15mg film-coated tablets. Last updated December 2014

10. National Institute for Health and Care Excellence (NICE). Clinical guideline 94 (CG94). Unstable Angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. 2010.

11. National Institute for Health and Care Excellence (NICE). Clinical Guideline 167 (CG167). Myocardial infarction with ST-segment elevation: the acute management of myocardial infarction with ST-segment elevation. 2013.

12. National Institute for Health and Care Excellence (NICE). Clinical Guideline 172 (CG172). Secondary prevention in primary and secondary care for patients following a myocardial infarction. 2013.

13. Windecker S, Kolh P, Alfonso F et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2014;35:2541–2619.

14. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Eur Heart J 2012;33:2569-619.

15. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32: 2999–3054

This assessment is based on data submitted by the applicant company up to and including 14 May 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.