Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

rivaroxaban 15 and 20mg film-coated tablets (Xarelto®) SMC No. (756/12)

Bayer PLC

13 January 2012

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 accepted for restricted use within NHS Scotland.

Indication under review: the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

SMC restriction: Rivaroxaban is accepted for use in patients who have poor INR control despite evidence that they are complying with a coumarin anticoagulant and in patients who are allergic to or unable to tolerate coumarin anticoagulants.

Rivaroxaban was non-inferior to standard oral anticoagulation at preventing stroke or systemic embolism in one large, double-blind study in patients with atrial fibrillation and moderate to high risk of stroke. This was not associated with a significantly increased risk of major or non-major clinically relevant bleeding.

The submitting company made an economic case for rivaroxaban use in the restricted patient population described above.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 13 February, 2012

Indication

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Dosing Information

The recommended dose is 20mg once daily. Therapy should be continued long-term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding. In patients with moderate to severe renal impairment, a dose of 15mg once daily is recommended.

Product availability date

19th December 2011

Summary of evidence on comparative efficacy

Rivaroxaban is a selective direct factor Xa inhibitor which interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting thrombin formation and the development of thrombi. Rivaroxaban has previously been accepted by the Scottish Medicines Consortium for use in the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery.

This submission is for a new indication; the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. The submitting company requested that SMC consider this product when positioned for use in patients who are either not well controlled on warfarin or in patients who are eligible for an oral anticoagulant but warfarin is inappropriate.

The key evidence to support this new indication for rivaroxaban comes from the ROCKET AF study.[1,2,3] This was a randomised, double-blind, double-dummy, phase III study comparing rivaroxaban with warfarin in 14,264 patients with non-valvular atrial fibrillation and moderate to high risk of stroke as a result of prior stroke, transient ischaemic attack (TIA), or systemic embolism, or at least two of the following risk factors: heart failure or left ventricular ejection fraction ≤35%, hypertension (systolic blood pressure ≥180mm Hg or diastolic blood pressure ≥100mm Hg), age ≥75 years or diabetes mellitus. The study design capped the proportion of enrolled patients with only two risk factors at 10%, so the majority of patients (90%) were required to have at least three risk factors, or a prior stroke, TIA or systemic embolism ($CHADS_2$ score ≥3). Patients were randomised (with stratification by country, prior use of vitamin K antagonist and history of stroke, TIA or non-CNS systemic embolism) to receive rivaroxaban 20mg daily (15mg daily in patients with creatinine clearance 30 to 49ml/min) or dose-adjusted warfarin to maintain an international normalised ratio (INR) of 2.0 to 3.0. Patients were permitted to receive aspirin <100mg daily for atrial fibrillation or atherosclerotic disease.[1,2]

The primary outcome was the composite of stroke or systemic embolism. The study primarily assessed the non-inferiority of rivaroxaban to warfarin using a non-inferiority margin of 1.46 with

a one-sided significance level of 0.025 for the relative risk of an outcome. If non-inferiority was confirmed, tests for superiority were performed. Clinical efficacy and safety events were adjudicated by an independent clinical endpoint committee. [1,2]

After a median duration of 590 days of treatment and 707 days of overall follow-up, the annual rates of the composite primary endpoint were 1.7% for rivaroxaban and 2.2% for warfarin. This met the pre-specified criteria for non-inferiority versus warfarin and superiority was demonstrated in the safety on-treatment population but not in the intention to treat overall follow-up population. [2,3] Details are given in the table below.

Table 1: Results of primary endpoint, its components and other key secondary endpoints [2,3]

	Rivaroxaban		**Warfarin**	
	No. of patients	Annual rate	No. of patients	Annual rate
Primary endpoint:				
Stroke/ systemic embolism in the per-protocol population	188/6958	1.7%	241/7004	2.2%
HR (95% CI) vs warfarin	0.79 (0.66 to 0.96) P<0.001 (for non-inferiority)			
Stroke/ systemic embolism in the safety on-treatment population	189/7061	1.7%	243/7082	2.2%
HR (95% CI) vs warfarin	0.79 (0.65 to 0.95) P=0.02			
Stroke/ systemic embolism in the intention to treat overall follow-up population	269/7081	2.1%	306/7090	2.4%
HR (95% CI) vs warfarin	0.88 (0.75 to 1.03) P=0.12			
Components of primary endpoint in the safety on-treatment population :				
Stroke (total)	184/7061	1.65%	221/7082	1.96%
HR (95% CI) vs warfarin	0.85 (0.70 to 1.03) P=0.092			
Ischaemic stroke	149/7061	1.34%	161/7082	1.42%
HR (95% CI) vs warfarin	0.94 (0.75 to 1.17) P=0.581			
Haemorrhagic stroke	29/7061	0.26%	50/7082	0.44%
HR (95% CI) vs warfarin	0.59 (0.37 to 0.93) P=0.024			
Systemic embolism	5/7061	0.04%	22/7082	0.19%
HR (95% CI) vs warfarin	0.23 (0.09 to 0.61) p=0.003			

Secondary endpoints:				
Stroke, systemic embolism and vascular death	346/7061	3.11%	410/7082	3.63%
HR (95% CI) vs warfarin	0.86 (0.74 to 0.99) p=0.034			
Stroke, systemic embolism, vascular death and MI	433/7061	3.91%	519/7082	4.62%
HR (95% CI) vs warfarin	0.85 (0.74 to 0.96) p=0.010			

HR: hazard ratio, CI: confidence interval, vs: versus, p-values for superiority over warfarin unless otherwise stated.

The rate of myocardial infarction was numerically, but not statistically significantly, lower in the rivaroxaban compared with the warfarin group.[2,3]

The treatment effect of rivaroxaban was similar across the various subgroup analyses.[2,3] In the subgroup of patients with moderate renal impairment (creatinine clearance 30 to 49ml/min), who received the lower dose of rivaroxaban (15mg daily), 21% of the overall population, a primary event occurred in 2.32% per year in the rivaroxaban group compared with 2.77% per year in the warfarin group: HR of 0.84 (95% CI: 0.57 to 1.23). There were however differences between this subgroup and the overall study population in terms of baseline characteristics.[4]

Analysis of treatment effect by quartiles of the time with an INR within the therapeutic range (TTR) in warfarin-treated patients found consistent results across the levels of INR control.[2,3]

Summary of evidence on comparative safety

The key safety outcome for any antithrombotic agent is the risk of bleeding. The primary safety outcome for rivaroxaban in ROCKET AF was the composite of major and non-major clinically relevant bleeding events. Major bleeding was defined as at least one of the following: associated with reduction in haemoglobin level of ≥2g/dL; leading to transfusion of ≥2 units of blood or packed cells or symptomatic in a critical area or organ such as intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding or fatal bleeding. Clinically relevant non-major bleeding was defined as overt bleeding not meeting the above major bleeding criteria but associated with medical intervention, contact with physician, temporary cessation of study medication, pain or impairment of daily activities.[1,2]

The annual rate of the primary safety outcome was not significantly different between the rivaroxaban and warfarin groups (see table 2). Each of the annual rates of critical, fatal and intracranial bleeding was significantly lower with rivaroxaban compared with warfarin. The incidence of transfusions and decreases in haemoglobin ≥2g/dL was significantly higher with rivaroxaban than warfarin. The annual rate of gastro-intestinal bleeding, including upper, lower and rectal bleeding, was significantly higher in the rivaroxaban group compared to warfarin.[2,3]

Table 2: results of the primary safety outcome and other bleeding events [2,3]

	Rivaroxaban (n=7,111)		Warfarin (n=7,125)	
	No. of patients	Annual Rate	No. of patients	Annual Rate
Major and non-major clinically relevant bleeding	1,475	14.9%	1,449	14.5%
HR (95% CI) vs warfarin	1.03 (0.96 to 1.11) P=0.44			
Any major bleeding	395	3.6%	386	3.4%
HR (95% CI) vs warfarin	1.04 (0.90 to 1.20) P=0.58			
Critical bleeding	91	0.8%	133	1.2%
HR (95% CI) vs warfarin	0.69 (0.53 to 0.91) P=0.007			
Fatal bleeding	27	0.2%	55	0.5
HR (95% CI) vs warfarin	0.50 (0.31 to 0.79) P=0.003			
Intra-cranial bleeding	55	0.5%	84	0.7%
HR (95% CI) vs warfarin	0.67 (0.47 to 0.93) P=0.02			
Gastro-intestinal bleeding (upper, lower and rectal)	224	NR	154	NR
HR (95% CI) vs warfarin	NR P<0.001			

HR: hazard ratio, CI: confidence interval, vs: versus, NR: not reported, p-values for superiority over warfarin unless otherwise stated.

Adverse events were reported in 81% (5,791/7,111) of rivaroxaban and 82% (5,810/7,125) of warfarin patients. The most frequently reported adverse events in the rivaroxaban group were epistaxis (10%), peripheral oedema (6.1%), and dizziness (6.1%), and in the warfarin group were epistaxis (8.6%), nasopharyngitis (6.4%) and dizziness (6.3%). Epistaxis and haematuria were significantly more frequent with rivaroxaban than warfarin (10% versus 8.6%, and 4.2% versus 3.4% respectively). The incidence of other reported adverse events was similar between groups. More rivaroxaban than warfarin treated patients discontinued treatment due to adverse events: 8.3% (594/7,131) versus 7.0% (498/7,133). Liver function test events reported as either alanine aminotransferase >3 times upper limit of normal (ULN) and total bilirubin >2 times ULN on same day occurred in 0.47% (33/7,111) of rivaroxaban and 0.50% (35/7,125) of warfarin patients.

Summary of clinical effectiveness issues

The pivotal study was a comparison with a relevant active comparator, warfarin, using a composite primary endpoint of direct health outcomes, stroke and systemic embolism. Rivaroxaban was non-inferior to warfarin, although the absolute difference was small (0.5%). However, there is some uncertainty around the subsequent superiority testing and whether or not superiority in an appropriate population has been demonstrated. Superiority was not demonstrated in the conventional intention-to-treat population. In this population, after early discontinuation of study drug there was a numerically higher primary event rate in the rivaroxaban than the warfarin group. Approximately half of the patients who discontinued the

study drug in both groups subsequently received open-label warfarin. However, there appeared to be sub-optimal conversion to a therapeutic INR in patients originally assigned to the rivaroxaban group.

The difference between the treatment groups in the composite endpoint was mainly driven by a reduction in the total rate of stroke. Although the rates numerically favoured rivaroxaban, the difference was only statistically significant for haemorrhagic stroke. Also numerically (but not significantly) fewer rivaroxaban than warfarin patients experienced death or disabling stroke.[2,3] This is relevant since patients with atrial fibrillation have a higher risk of disabling and recurrent stroke and mortality from atrial fibrillation related stroke than from other causes. The annual rate of myocardial infarction was numerically, but not significantly, lower in the rivaroxaban compared with the warfarin group.

The study excluded patients who had a recent stroke (any stroke within 14 days and severe, disabling stroke within 3 months) or were at high risk of bleeding. During the pivotal study, the INR was within the therapeutic range for, on average, 55% of the time in warfarin-treated patients. This is lower than rates reported in other studies but there are differences in how the rates were calculated and in the study populations. An analysis of study outcomes in relation to each study centre's mean time in therapeutic range for the warfarin group (according to four quartiles), indicated that the observed benefits of rivaroxaban compared to warfarin were similar across the range of INR control.[2,3]

Concomitant use of aspirin (<100mg daily) was permitted during the study and at baseline was used by approximately 36% of patients in each group.[1,2] This increased the risk of bleeding in these patients.

During the pivotal study, rivaroxaban was associated with a significantly higher rate of gastro-intestinal bleeding, including upper, lower and rectal bleeding, compared to warfarin.[2,3] It is unclear how rivaroxaban would affect patients susceptible to gastro-intestinal adverse events in clinical practice. Although there was no difference between rivaroxaban and warfarin in terms of effects on liver function during the pivotal study, longer term data are required. [2,3]

There is no specific antidote to rivaroxaban and, since it acts at a different step in the coagulation cascade from warfarin, the standard strategies used to reverse warfarin are not appropriate. Rivaroxaban discontinuation and supportive measures are initially recommended in patients who bleed. This may also be an issue in patients who require emergency surgery. The SPC advises that rivaroxaban should be stopped at least 24 hours before an invasive procedure or surgical intervention, if possible and based on the clinical judgement of the physician.

Warfarin has a narrow therapeutic margin which requires monitoring to maintain an INR within the desired therapeutic range. In addition, warfarin is associated with many drug and dietary interactions which can make therapy difficult to control. Poor control can lead to an increased risk of stroke in patients with a low INR or an increased risk of bleeding and associated hospitalisation in patients with an INR above the therapeutic range. Rivaroxaban requires no therapeutic monitoring which would reduce the workload of services associated with warfarin monitoring and potentially reduce the risk of poor control to the patient. Rivaroxaban is associated with fewer interactions than warfarin but it should be taken with food.

The submitting company has requested that SMC considers rivaroxaban when positioned for use in patients who are not well controlled on warfarin and in patients who are eligible for an oral anticoagulant but warfarin is inappropriate. Clinical data to support this positioning are

limited. The consistency of treatment effect across the quartiles of TTR in warfarin-treated patients was used to indicate efficacy in patients not well controlled on warfarin. There are no data to support use in patients unsuitable for warfarin, who would currently receive aspirin or no treatment although a proportion of the patients in the studies used in the network meta-analysis may have been in this category.

There are no comparative data with other newer anticoagulants. An indirect comparison in the form of a network meta-analysis was presented to allow comparison with aspirin and no treatment, and the submitting company suggests that this supports use in patients unsuitable for warfarin. However, it was not necessary for patients in the studies used in the network meta-analysis to be unsuitable for warfarin. Although results were also available versus dabigatran, these were not used in the economic case as dabigatran was not considered a comparator since it is not currently in routine use in Scotland. The base case analysis of the network meta-analysis was performed in the safety on-treatment population results of ROCKET AF (which demonstrated superiority of rivaroxaban over warfarin in terms of stroke and systemic embolism) and the intention-to-treat populations of the others studies. Sensitivity analysis used the intention-to-treat population from ROCKET AF.

Rivaroxaban may offer some benefits in patient administration as it is taken once daily whereas dabigatran requires twice daily dosing. In addition, rivaroxaban is less dependent on renal excretion than dabigatran.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis in two scenarios:

- Scenario 1: Patients who are not well controlled on warfarin – in this scenario, the comparator was warfarin.
- Scenario 2: Patients who are eligible for an oral anticoagulant but warfarin is inappropriate or contraindicated. In this scenario the comparator was either aspirin or no anticoagulant.

According to SMC policy, dabigatran was not considered in the submission on the basis that its use is not current practice in Scotland.

The analysis was carried out using a Markov model, run over the lifetime of a typical patient, and including health states based on the key endpoints of the clinical trial such as ischaemic stroke, intracranial haemorrhage, systemic embolism, bleeding other than in the head, and myocardial infarction. Changes in the rate of events as a result of switching to rivaroxaban came from the main clinical study, ROCKET-AF, for the comparison with warfarin and from the network meta-analysis for the comparison with aspirin and no anticoagulation treatment.

Mortality rates following events were taken from published clinical studies. Utility values for atrial fibrillation and following events were also taken from published studies. No disutility was applied for being on warfarin treatment.

Costs of the medicines also covered the costs of INR monitoring while on warfarin. Based on data from a secondary care clinic, it was assumed that after patients had been initiated on

treatment because they were poorly controlled they would need 36 monitoring visits per annum. Most of these visits would take place in primary care.

Discontinuation rates for treatment were taken from clinical trials.

Costs of events were taken from NHS Reference Costs; while in several cases equivalent Scottish data were available, the sensitivity analysis suggests the precise figures used are not key drivers of the results.

The company's base case results were as follows:

	Lifetime NHS/ social service costs	**Incremental life years**	**Incremental quality adjusted life years (QALYs)**	**Incremental cost per QALY gained**
Scenario 1- patients not well controlled on warfarin	-£1,589	0.087	0.073	Rivaroxaban dominates warfarin
Scenario 2a- patients unsuitable for warfarin, comparator= aspirin	£883	0.369	0.424	£2,083
Scenario 2b- patients unsuitable for warfarin, comparator= no treatment	£496	0.498	0.548	£906

An extensive one-way sensitivity analysis and a probabilistic sensitivity analysis (PSA) were carried out. For Scenario 1 the key sensitivity was to the number of INR monitoring visits while on warfarin and to a slightly lesser extent the cost per monitoring visit. Discontinuation rates for the two medicines also played a role, presumably reflecting how much less effective second line treatment was. The PSA was said to show an 88.6% chance rivaroxaban was dominant.

For scenarios 2a and 2b the key sensitivities were the relative risks with rivaroxaban compared to aspirin or no treatment in terms of reducing intracranial haemorrhage and ischaemic stroke.

The PSA showed an approximately 90% chance it would be cost-effective at a level of £30k per QALY in both scenarios.

One concern was that the economics model used differences in clinical event rates that were not statistically significant in the RCT. The company provided analyses excluding these and showed that it made very little difference to the results: in the comparison with warfarin the added cost was -£1,482 and the QALY gain 0.039, so rivaroxaban was still predicted to be dominant.

Another concern was that 36 INR monitoring visits per year was too high; while some patients on warfarin undoubtedly have this level of testing, it seems less plausible that this level would

be maintained for several years. The company provided additional analyses based on the intention to treat populations, which excluded clinical event rate differences that did not achieve statistical significance and lowered the assumed rate of INR testing. This showed that when the testing rate fell to 20 per year the cost per QALY was £17,927. This level of INR testing seemed more plausible.

Despite some uncertainties and limitations of the analysis, the economic case has been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- The Stroke Association
- AntiCoagulation Europe

Additional information: guidelines and protocols

The European Society of Cardiology (ESC) published "Guidelines for the management of atrial fibrillation" in 2010. This recommends antithrombotic use according to stroke risk stratification. Major risk factors include prior stroke or TIA, or thromboembolism and older age (≥75years). Clinically relevant non-major risk factors include heart failure, moderate to severe left ventricular systolic dysfunction, hypertension, diabetes mellitus, female sex, age 65 to 74 years, vascular disease (specifically prior myocardial infarction, peripheral artery disease, aortic plaque). For patients with one major or ≥two clinically relevant non-major risk factors, the guideline recommends antithrombotic therapy with an anticoagulant such as warfarin (INR 2.0 to 3.0; target 2.5). For patients with one clinically relevant non-major risk factor, the guideline recommends preferably an anticoagulant (as above) or aspirin 75 to 325mg daily. For patients with no risk factors, the guideline recommends preferably no antithrombotic therapy or aspirin 75 to 325mg daily. The guideline also states that new oral anticoagulants which may be viable alternatives to a vitamin K antagonist, e.g. dabigatran, may ultimately be considered with recommendations for thromboprophylaxis taking into account stroke and bleeding risk stratification.

The National Institute for Health and Clinical Excellence published clinical guideline 36 "The management of atrial fibrillation" in June 2006. A risk-benefit assessment should be performed to categorise risk of stroke or thromboembolism into:

- High risk - previous ischaemic stroke/TIA or thromboembolic event; age ≥75years with hypertension, diabetes or vascular disease; clinical evidence of valve disease, heart failure or impaired left ventricular function on echocardiography. These patients should be prescribed warfarin to reach a target INR of 2.5 (range 2.0 to 3.0). If warfarin is contra-indicated then aspirin 75 to 300mg day should be prescribed.
- Moderate risk – age ≥65years with no high risk factors; age <75 years with hypertension, diabetes or vascular disease. These patients should be considered for anticoagulation with warfarin or aspirin 75 to 300mg daily.
- Low risk – age <65 years with no moderate or high risk factors. These patients should be prescribed aspirin 75 to 300mg daily.

This clinical guideline was reviewed in August 2011 and an update is expected in June 2014.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 36 "Antithrombotic Therapy" in March 1999 which includes a section on atrial fibrillation: prophylaxis of systemic embolism. This guideline is currently being updated and is expected to be published in autumn 2011.

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) published a "Focused update on the management of patients with atrial fibrillation (update on dabigatran)" in March 2011. The guideline update recommended that dabigatran is a useful alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolisation who do not have a prosthetic heart valve or haemodynamically significant valve disease, severe renal failure or advanced liver disease (impaired baseline clotting function). The guideline notes that because of the twice daily dosing and greater risk of non-haemorrhagic side effects with dabigatran, patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran. Selection of patients with AF and at least one additional risk factor for stroke who could benefit from treatment with dabigatran as opposed to warfarin should consider individual clinical features, including the ability to comply with twice daily dosing, availability of an anticoagulation management program to sustain routine monitoring of INR, patient preferences, cost and other factors.

Healthcare Improvement Scotland publishes a consensus statement "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation" in October 2011. This statement states that on balance of risks and benefits, warfarin remains the anticoagulant of clinical choice for moderate or high risk atrial fibrillation patients (CHA_2DS_2-VASc≥2) with good INR control and clinicians should consider prescribing dabigatran in patients with poor INR control despite evidence that they are complying or allergy to or intolerable side effects from coumarin anticoagulants".

Additional information: comparators

Comparators will depend on stroke risk assessment and will include warfarin and aspirin. Dabigatran has also recently been accepted for use by SMC.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Rivaroxaban	**20mg orally daily**	**764**
Dabigatran	110 or 150mg orally twice daily	917
Warfarin	Orally as determined by prothrombin time	13 to 39
Aspirin	75 to 300mg orally daily	4 to 22

Doses are for general comparison and do not imply therapeutic equivalence. Costs for rivaroxaban are taken from the company submission. Costs for warfarin and aspirin are from eVadis on 7 November 2011.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 61,076 (with atrial fibrillation, matching license) of whom 22.7% would fit the company's proposed positioning (i.e. poorly controlled on warfarin or warfarin inappropriate). Based on an estimated uptake of 6% in year 1 and 60% in year 5, the gross impact on the medicines budget was estimated at £602K in year 1 and £6,186K in year 5. Savings on the medicines budget would be in terms of warfarin and aspirin avoided only. The net medicines budget impact was estimated at £582K and £5,982K. Note that this does not include the impact on INR monitoring or use of other NHS services (e.g. strokes avoided).

A more realistic overview of the budget impact of new antithrombotic treatments in atrial fibrillation would be obtained by taking into consideration all of the currently available treatment options, including dabigatran.

References

The undernoted references were supplied with the submission.

1. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. Am Heart J 2010 Mar;159(3):340-7.

2. Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med 2011;365:883-91.

3. Patel MR, Mahaffey KW, Garg J et al. Supplementary Appendix to Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.

4. Fox KA, Piccini JP, Wojdyla D et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J 2011;32:2387-94.

This assessment is based on data submitted by the applicant company up to and including 12 December 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.