Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Angela Timoney FRPharmS
NHS SCOTLAND

apixaban 2.5mg and 5mg film-coated tablets (Eliquis®) SMC No. (836/13)

Bristol-Myers Squibb / Pfizer

11 January 2013

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

apixaban (Eliquis®) is accepted for use within NHS Scotland.

Indication under review: for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA class ≥II).

Apixaban was superior to standard oral anticoagulation at preventing stroke or systemic embolism in one large, double-blind study in patients with atrial fibrillation and at least one risk factor for stroke. It was also associated with a significant reduction in risk of major bleeding.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA class ≥II).

Dosing Information

The recommended dose is 5mg orally twice daily, swallowed whole with water, with or without food. In patients with at least two of the following characteristics the recommended dose is 2.5mg twice daily: age ≥80 years, bodyweight ≤60kg or serum creatinine ≥1.5mg/dL (133micromole/L). Patients with exclusive criteria of severe renal impairment (creatinine clearance 15-29 ml/min) should also receive the lower dose of apixaban 2.5mg twice daily.

Product availability date

12 December 2012

Summary of evidence on comparative efficacy

Apixaban 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. Apixaban has previously been accepted by the Scottish Medicines Consortium for use in the prevention of venous thromboembolic events (VTE) in adult patients who have undergone 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 key evidence to support this indication for apixaban comes from results of two randomised, double-blind, double-dummy, phase III studies in patients with non-valvular atrial fibrillation: ARISTOTLE (versus warfarin) and AVERROES (versus aspirin).[1,2,3,4]

The ARISTOTLE study included 18,201 adults with atrial fibrillation or flutter and at least one of the following risk factors for stroke: age ≥75 years, previous stroke, transient ischaemic attack or systemic embolism, symptomatic congestive heart failure within the previous 3 months or left ventricular ejection fraction ≤40%, diabetes mellitus or hypertension requiring treatment. Both warfarin-naïve and warfarin-experienced patients were enrolled with an aim of including at least 40% warfarin-naïve patients. Patients were randomised (with stratification by site and prior use of vitamin K antagonist [VKA]) to receive apixaban 5mg twice daily (2.5mg twice daily in patients with two or more of these criteria: age ≥80 years, body weight ≤ 60kg or serum creatinine ≥1.5mg/dL) or dose-adjusted warfarin to maintain an international normalised ratio (INR) of 2.0 to 3.0. Patients were permitted to receive aspirin ≤165mg daily.[1,2]

The primary outcome was the composite of stroke or systemic embolism and ARISTOTLE was designed to initially assess the non-inferiority of apixaban to warfarin and, if confirmed, tests for superiority were performed.

After a median duration of follow-up of 1.8 years, the annual rates of the composite primary endpoint were 1.27% for apixaban and 1.60% for warfarin, meeting the pre-specified criteria for non-inferiority and demonstrating superiority over warfarin. Details are given in the table below with p-values representing superiority test results.

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

	ARISTOTLE study			
	Apixaban (n=9,120)		Warfarin (n=9,081)	
	No of patients	Annual rate	No of patients	Annual rate
Primary endpoint				
Stroke or systemic embolism	212	1.27%	265	1.60%
HR (95% CI) versus warfarin	0.79 (0.66 to 0.95) p=0.01			
Components of primary endpoint:				
Stroke (total)	199	1.19%	250	1.51%
HR (95% CI) versus warfarin	0.79 (0.65 to 0.95) p=0.01			
Ischaemic or unspecified stroke	162	0.97%	175	1.05%
HR (95% CI) versus warfarin	0.92 (0.74 to 1.13) p=0.42			
Haemorrhagic stroke	40	0.24%	78	0.47%
HR (95% CI) versus warfarin	0.51 (0.35 to 0.75) p<0.001			
Systemic embolism	15	0.09%	17	0.10%
HR (95% CI) versus warfarin	0.87 (0.44 to 1.75) p=0.70			
Other secondary outcomes				
Death from any cause	603	3.52%	669	3.94%
HR (95% CI) versus warfarin	0.89 (0.80 to 0.998) p=0.047			
Net clinical benefit: stroke, systemic embolism or major bleeding	521/9,088	3.17%	666/9,052	4.11%
HR (95% CI) versus warfarin	0.77 (0.69 to 0.86) p<0.001			
Net clinical benefit: stroke, systemic embolism, major bleeding or death from any cause	1,009/9,088	6.13%	1,168/9,052	7.20%
HR (95% CI) versus warfarin	0.85 (0.78 to 0.92) p<0.001			

HR: hazard ratio, CI: confidence interval, p-values for superiority over warfarin

The AVERROES study included 5,599 patients aged at least 50 years who had atrial fibrillation and at least one of the following risk factors for stroke: age ≥75 years, previous stroke or transient ischaemic attack, heart failure (New York Heart Association class ≥II), left ventricular ejection fraction ≤35%, diabetes mellitus (receiving treatment), arterial hypertension (receiving treatment) or peripheral arterial disease. Eligible patients had failed or were unsuitable for VKA therapy. Patients were randomised to receive apixaban 5mg twice daily (or 2.5mg twice daily as before) or aspirin 81mg to 324mg daily, with dose at the discretion of local investigator. After a mean follow-up of 1.1 years, a planned interim analysis found a significant treatment benefit in favour of apixaban and the study was stopped early. The results at this time form the primary analysis.

In an intent-to-treat analysis, the primary outcome of stroke or systemic embolism occurred in 51/2,808 apixaban patients (1.6% per year) compared with 113/2,791 aspirin patients (3.7% per year): HR 0.45 (95% CI: 0.32 to 0.62) (p<0.001). The difference between the groups in the composite primary endpoint was mainly driven by a reduction in the rate of stroke, particularly ischaemic stroke (1.1% per year versus 3.0% per year, respectively, corresponding to a HR of 0.37 [95% CI: 0.25 to 0.55], p<0.001). Apixaban was significantly more effective than aspirin in

terms of total stroke (1.6% versus 3.4% per year respectively: HR 0.46 [95% CI: 0.33 to 0.65]), ischaemc stroke (1.1% versus 3.0% per year respectively: HR 0.37 [95% CI: 0.25 to 0.55]), disabling or fatal stroke (1.0% versus 2.3% per year respectively: HR 0.43 [95% CI: 0.28 to 0.65]) and systemic embolism (0.1% versus 0.4% per year respectively: HR 0.15 [95% CI: 0.03 to 0.68]). The composite of stroke, systemic embolism or death also significantly favoured apixaban (4.6% versus 7.2% per year respectively: HR 0.64 [95% CI: 0.51 to 0.78]).

Summary of evidence on comparative safety

The key safety outcome for an antithrombotic agent such as apixaban is the risk of bleeding. In the ARISTOTLE study, the primary safety outcome was major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria (acute or sub-acute clinically overt bleeding accompanied by at least one of the following: reduction in haemoglobin level of ≥2g/dL , transfusion of ≥2 units of packed red blood cells, bleeding that was fatal or occurred in the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal). This was assessed in patients who had received at least one dose of study drug and included events from the start to 2 days after the last dose. As illustrated in the table below, the annual rate of major bleeding was significantly lower with apixaban compared with warfarin. Each of the annual rates of intra-cranial bleeding, major or clinically relevant non-major bleeding and any bleeding were significantly lower with apixaban than warfarin (p<0.001).[2]

Table 2: Results of key safety endpoints[2]

	ARISTOTLE study			
	Apixaban (n=9,088)		Warfarin (n=9,052)	
	No of patients	Annual rate	No of patients	Annual rate
Major bleeding	327	2.13%	462	3.09%
HR (95% CI) versus warfarin	0.69 (0.60 to 0.80) p<0.001			
Intra-cranial bleeding	52	0.33%	122	0.80%
HR (95% CI) versus warfarin	0.42 (0.30 to 0.58) p<0.001			
Gastro-intestinal bleeding	105	0.76%	119	0.86%
HR (95% CI) versus warfarin	0.89 (0.70 to 1.15) p=0.37			
Major or clinically relevant non-major bleeding	613	4.07%	877	6.01%
HR (95% CI) versus warfarin	0.68 (0.61 to 0.75) p<0.001			
Any bleeding	2,356	18.1%	3,060	25.8%
HR (95% CI) versus warfarin	0.71 (0.68 to 0.75) p<0.001			

HR: hazard ratio, CI: confidence interval, p-values for superiority over warfarin

Adverse events were reported in 81% (7,406/9,088) apixaban and 83% (7,521/9,052) of warfarin patients. The incidence of other reported adverse events was similar between groups. Serious adverse events were reported in 35% (3,182/9,088) and 36% (3,302/9,052) of patients respectively. The only serious adverse events reported in ≥1% of patients in either group were atrial fibrillation in 3.3% (301/9,088) of apixaban and 3.2% (287/9,052) of warfarin patients and pneumonia in 2.2% (202/9,088) and 2.6% (231/9,052) patients respectively. Discontinuation due to an adverse event was reported in 7.6% (688/9,088) and 8.4% (758/9,052) of patients respectively.[2]

In the AVERROES study, major bleeding (as defined previously) was numerically higher in the apixaban than aspirin group: 1.4% per year compared with 1.2% per year (HR 1.13 [95% CI: 0.74 to 1.75], p=0.57). The incidences of intra-cranial, gastro-intestinal and fatal bleeding were similar in both groups. Clinically relevant non-major bleeding (3.1% versus 2.7% per year in the apixaban and aspirin groups, respectively) and minor bleeding (6.3% versus 5.0% per year in the respective groups) were numerically higher in the apixaban group.[4]

In both studies, safety results for effects on liver function were similar between groups.

Summary of clinical effectiveness issues

The pivotal studies compared apixaban with warfarin and aspirin using a composite primary endpoint of direct health outcomes, stroke and systemic embolism. Apixaban was superior to both warfarin and aspirin, although the absolute difference compared with warfarin was small (0.33% per year).[2] The difference between groups in the composite endpoint was primarily due to the reduction in stroke, mainly haemorrhagic stroke when compared with warfarin and mainly ischaemic stroke when compared with aspirin. Since patients with atrial fibrillation have a higher risk of disabling and recurrent stroke and mortality from stroke than from those with stroke related to other causes, reductions in stroke rate are clinically important. Notably, apixaban also significantly reduced the incidence of death from any cause compared with warfarin.[2]

The ARISTOTLE study excluded patients who had a recent stroke or were at high risk of bleeding. During this study, the INR was within the therapeutic range for, on average, 62% of the time in warfarin-treated patients. Although this is similar to rates reported in other studies and is reflective of clinical practice, individual patient variation is acknowledged. An analysis of the primary outcome 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 apixaban compared to warfarin were similar across the range of INR control.

Concomitant use of aspirin (≤165mg daily) was permitted during the ARISTOTLE study and at baseline was used by approximately 31% of patients in each group and this could have increased the risk of bleeding in these patients.[2]

Although there was no difference between apixaban and warfarin or aspirin in terms of effects on liver function during the pivotal studies, longer term data are required.[2,4]

The AVERROES study had a number of limitations with respect to current practice. It included patients who had failed or were unsuitable for VKA therapy, which is narrower than the licensed population for apixaban. While there may still be some use of aspirin in clinical practice, current guidelines only recommend the use of aspirin in patients who refuse any oral anticoagulant therapy, and patients unsuitable for VKA therapy would more likely be treated with a new oral anticoagulant.[5,6] The dose of aspirin used varied widely from 81mg to 324mg daily. The study had a shorter than planned follow-up after being stopped early because of the finding of a significant treatment benefit at a planned interim analysis.

There is no specific antidote to apixaban and, since it acts at a different step in the coagulation cascade from warfarin, the standard strategies used to reverse warfarin are not appropriate. Apixaban 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 apixaban should be stopped at least 24 hours before elective surgery or invasive procedures with a low risk of bleeding, and at least 48 hours before those at moderate or high risk of bleeding.

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. Apixaban requires no therapeutic monitoring which would reduce the workload of services associated with warfarin monitoring and potentially reduce the risks to the patient associated with poor INR control. Apixaban is associated with fewer interactions than warfarin. Apixaban, like dabigatran, has a twice daily dosing regimen. Rivaroxaban has a once daily dosing regimen.

There are no comparative data with newer anticoagulants. An indirect comparison, in the form of two Bayesian network meta-analyses (NMA), was presented to allow comparison with dabigatran and rivaroxaban: one in patients who were suitable for VKA treatment and one in patients for whom VKA treatment was considered unsuitable. The NMA in VKA-suitable patients included three studies: ARISTOTLE (apixaban versus warfarin)[2], RE-LY (dabigatran versus warfarin)[7,8] and ROCKET-AF (rivaroxaban versus warfarin).[9] The NMA in VKA-unsuitable patients included these three studies plus AVERROES (apixaban versus aspirin).[4] The base-case analysis used the original results reported for the RE-LY study (2009).[7] However, sensitivity analysis used updated RE-LY results (2010) and ROCKET-AF ITT results which were considered more appropriate.[8] The primary efficacy outcome analysed was the composite of stroke or systemic embolism and the primary safety outcome was major bleeding, but other secondary efficacy and safety outcomes were also analysed. There were a number of important differences between the studies including mean $CHADS_2$ scores, previous history of stroke, TIA or systemic embolism, proportions of patients previously treated with VKA and proportion of patients receiving aspirin. There were also differences in the time in the therapeutic range for warfarin-treated patients. However, the results suggest that there was no significant difference between apixaban and dabigatran and rivaroxaban in any of the efficacy outcomes in VKA-suitable and unsuitable patients. The results also suggest that apixaban was associated with significantly less major bleeding, gastrointestinal bleeding and any bleeding than dabigatran and rivaroxaban. The results for VKA-suitable patients are consistent with two recently published indirect comparisons.[10,11] The results for VKA-unsuitable patients are less robust given that the analysis included patients both suitable and unsuitable for warfarin.

Summary of comparative health economic evidence

The submitting companies presented a lifetime cost-utility model investigating the use of apixaban in two distinct patient groups:

- Vitamin K agonist (VKA)-suitable patients (patients who are suitable for warfarin). In this analysis the comparator treatments were warfarin, dabigatran 110mg, dabigatran 150mg/110mg sequence and rivaroxaban.
- VKA-unsuitable patients (patients who are demonstrated and/or expected to be unsuitable for warfarin). The comparators in this analysis were aspirin, dabigatran 110mg, dabigatran 150mg/110mg sequence and rivaroxaban.

A Markov model was used and included 18 relevant health states including ischaemic stroke (mild, moderate, severe), haemorrhagic stroke (mild, moderate, severe), systemic embolism, myocardial infarction, AF without original anticoagulation (for patients who may withdraw from treatment/go on to antiplatelet treatment) and bleeding events. Patients could move on to alternative second-line treatment options in the event of suffering an event or side effect of treatment.

Data from the ARISTOTLE and AVERROES studies were used in two network meta-analyses (NMA) in order to estimate the clinical outcomes of each treatment option. The base case economic result did not use the RE-LY 2010 results in the NMA. The model assumed that the benefits of each treatment continued for as long as the patient remained on the therapy, as with other economic models in this area.

Utilities were estimated from literature sources. Utility values took account of events such as MI and stroke, adverse events (bleeds, CV hospitalisations) and also a utility decrement applied for the duration of treatment. This decrement was the same for aspirin, dabigatran, rivaroxaban and apixaban (0.002) but higher for warfarin (0.013), with the estimates taken from a published paper. Resource use was estimated from a range of published sources. Monitoring costs for warfarin treatment was estimated at £200 in the base case.

The base case results for the VKA-suitable patients indicated a cost per quality adjusted life year (QALY) for apixaban versus warfarin of £12,119 based on an incremental cost of £1,877 and a QALY gain of 0.155. All other comparator treatments were ruled out of the incremental analysis due to dominance or extended dominance.

The base case results for the VKA-unsuitable patients showed a cost per QALY for apixaban compared to dabigatran 150mg/110mg of £13,467, based on an incremental cost of £606 and a QALY gain of 0.045. Dabigatran 110mg and rivaroxaban were excluded on the basis of dominance or extended dominance in the incremental analysis.

Extensive sensitivity analyses were presented and the results remained relatively stable and under £20,000 per QALY for most analyses. Analysis was provided to show the impact of removing the disutility associated with warfarin and comparator treatments to bring it into line with other SMC submissions in this area, and this had the effect of increasing the cost per QALY to £16,903.

A number of issues were noted with the analysis:

- The base case results included some non-significant differences in outcomes from the NMA. Additional analyses were provided by the submitting companies to show the effect of removing these differences. In the VKA-suitable group, this increased the cost per QALY to £13,281. If the warfarin disutilities were also removed from this analysis, the cost per QALY rose to £18,335. In the VKA-unsuitable group, the incremental analysis changed to give a cost per QALY of apixaban versus rivaroxaban (the next most effective treatment in the revised incremental analysis) of £10,481.
- As noted above, there were some limitations associated with the indirect comparison: for example, the VKA-unsuitable NMA included some patients who were VKA-suitable. In addition, revised analysis was provided by the company to show the impact of including the RE-LY 2010 results in the NMA. While this altered the costs and QALYs for the dabigatran regimens in the VKA-suitable patients, the cost per QALY of apixaban versus

warfarin remained unchanged in the base case incremental analysis and in the sensitivity analysis where non-significant differences were removed.

- Other SMC submissions in this area have included a 'no treatment' comparator to recognise that there may be a group of patients who do not currently receive any active treatment. Revised analysis was provided to include a 'no treatment' option but it did not alter the overall findings as 'no treatment' was a dominated therapy strategy.

While there may be some limitations associated with the analysis, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was made by Anticoagulation Europe.

Additional information: guidelines and protocols

SIGN published guideline number 129 "Antithrombotics: indications and management. A national clinical guideline" in August 2012.[5] This includes a section on atrial fibrillation: prophylaxis of systemic embolism. This recommends that all patients with atrial fibrillation who have a $CHADS_2$ or CHA_2DS_2-VASc score of ≥1 (one or more clinically relevant risk factors) should be considered for warfarin at a target INR of 2.5 (range 2.0-3.0) or a newer anticoagulant. The balance of risks and benefits of anticoagulant therapy should be assessed and discussed annually with the patient, with consideration given to patient preference. Dabigatran and rivaroxaban can be considered as alternatives to warfarin in the management of patients with atrial fibrillation with one or more risk factor for stroke. Antiplatelet therapy should only be considered where warfarin or one of the alternative new anticoagulants has been declined. The guideline predates the licensing of apixaban for this indication.

NICE published clinical guideline (CG) 36 "Atrial fibrillation: The management of atrial fibrillation" in June 2006.[12] In patients with paroxysmal, persistent or permanent AF, 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 LV function on echocardiography. These patients should be prescribed adjusted-dose warfarin to reach a target INR of 2.5 (range 2.0 to 3.0). If warfarin is contra-indicated then aspirin 75mg 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 adjusted-dose warfarin or aspirin 75mg to 300mg daily.

Low risk – age <65 years with no moderate or high risk factors. These patients should be prescribed aspirin 75mg to 300mg daily.

This clinical guideline was reviewed in August 2011 and an update is underway with the publication date to be confirmed. NICE are in the process of developing a Single Technology

Appraisal "stroke and systemic embolism (prevention non-valvular atrial fibrillation) – apixaban" which is expected to be published in April 2013.

European Society of Cardiology (ESC) published "2012 focused update of the ESC guidelines for the management of atrial fibrillation" in 2012.[6] This recommends use of the CHA_2DS_2-VASc assessment which categorises risk into:

- major risk factors: prior stroke or TIA, or thromboembolsim and older age (≥75years).
- clinically relevant non-major risk factors: heart failure, moderate to severe left ventricular systolic dysfunction (e.g. LVEF ≤40%), hypertension, diabetes mellitus, female sex, age 65 to 74 years, vascular disease (specifically prior myocardial infarction, peripheral artery disease, aortic plaque).

For patients with a CHA_2DS_2-VASc score ≥2, the guideline recommends oral anticoagulant therapy with adjusted dose VKA (INR 2 to 3) or a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (rivaroxaban or apixaban) unless contra-indicated. For patients with a CHA_2DS_2-VASc score of 1, the guideline recommends that oral anticoagulant therapy with adjusted dose VKA (INR 2 to 3) or a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (rivaroxaban or apixaban) should be considered based upon assessment of the risk of bleeding complications and patient preferences. For patients with a CHA_2DS_2-VASc score of 0 (i.e. aged <65 years with lone atrial fibrillation) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended. Female patients who are aged <65 years and have lone atrial fibrillation (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered. When patients refuse any oral anticoagulant therapy, antiplatelet therapy should be considered using combination therapy with aspirin 75mg to 100mg plus clopidogrel 75mg daily (where there is a low risk of bleeding) or, less effectively, aspirin 75mg to 325mg daily. When oral anticoagulant therapy is recommended, a newer agent:

- Is recommended in patients having difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs or unable to attend or undertake INR monitoring.
- Should be considered rather than adjusted-dose VKA for most patients with non-valvular atrial fibrillation based on their net clinical benefit.

Assessment of risk of bleeding is recommended (using the HAS-BLED score) when prescribing antithrombotic therapy (VKA, newer oral anticoagulant therapy, aspirin/clopidogrel or aspirin).

The ACCF/AHA published a "Focused update on the management of patients with atrial fibrillation (update on dabigatran)" in March 2011.[13] 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 (creatinine clearance <15ml/min) 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 published a consensus statement "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation" in April 2012.[14] This statement advises 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 or rivaroxaban 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

Warfarin, dabigatran and rivaroxaban. Aspirin may be a comparator in patients who refuse warfarin or a newer oral anticoagulant.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
apixaban	**2.5mg or 5mg orally twice daily**	**800**
dabigatran	110mg or 150mg orally twice daily	800
rivaroxaban	15mg or 20mg orally daily	764
warfarin	Orally as determined by prothrombin time	4 to 15
aspirin	75mg to 300mg orally daily	4 to 10

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 25 October 2012 and MIMS November 2012. date.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 54,538 in year 1 rising to 55,586 in year 5, with an estimated uptake rate of 0.55% in year 1 and 12.50% in year 5.

The company provided 4 scenarios showing the effect of displacing warfarin in various proportions. In all cases, the gross impact on the medicines budget was estimated at £241k in year 1 and £5.579m in year 5. Net medicines budget impact estimates were provided for the following 4 scenarios where the use of other medicines was assumed to be displaced by apixaban:

- 0% displacement of warfarin and 100% displacement between dabigatran and rivaroxaban
    - The net medicines budget impact is expected to be £3k in year 1 and £106k.
- 6% displacement of warfarin and 94% displacement between dabigatran and rivaroxaban
    - The net medicines budget impact is expected to be £15k in year 1 and £400k.
- 25% displacement of warfarin and 75% displacement between dabigatran and rivaroxaban
    - The net medicines budget impact is expected to be £58k in year 1 and £1.4m.

- 50% displacement of warfarin and 50% displacement between dabigatran and rivaroxaban
    - The net medicines budget impact is expected to be £115k in year 1 and £2.7m.

SMC noted that the current uptake of newer anticoagulants may be lower than figures in the last bullet above and in practice the likely net budget impact may be higher than any of the estimates presented by the submitting company.

References

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

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This assessment is based on data submitted by the applicant company up to and including 17 December 2012.

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.