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 Jonathan G Fox

edoxaban tosilate15mg, 30mg and 60mg film-coated tablets (Lixiana®)
SMC No. (1095/15)

Daiichi Sankyo UK Limited

9 October 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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

edoxaban (Lixiana®) is accepted for use within NHS Scotland.

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

One phase III study showed non-inferiority of edoxaban versus a vitamin K antagonist for the prevention of stroke and systemic embolism in adult patients with NVAF and a $CHADS_2$ score of ≥2. It was also associated with a significant reduction in risk of major bleeding.

Chairman,
Scottish Medicines Consortium

Indication

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

Dosing Information

Edoxaban 60mg once daily and therapy should be continued long term.

Edoxaban 30mg once daily is recommended in patients with one or more of the following clinical factors:

- Moderate or severe renal impairment (creatinine clearance 15 to 50mL/min)
- Low body weight ≤60kg
- Concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole

Edoxaban 15mg once daily is only indicated when switching from edoxaban 30mg (in patients with one or more clinical factors for increased exposure) to a vitamin K antagonist together with an appropriate vitamin K antagonist dose.

Product availability date

July 2015

Summary of evidence on comparative efficacy

Edoxaban is a direct factor Xa inhibitor which, in the coagulation cascade, reduces thrombin generation, prolongs clotting time and reduces the risk of thrombus formation.[1] Edoxaban is licensed 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 congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA). It is the third oral direct factor Xa inhibitor to be licensed for this indication. The oral direct factor Xa inhibitors, rivaroxaban and apixaban, and the direct thrombin inhibitor, dabigatran, are also licensed for this indication. Dabigatran and apixaban have been accepted for use by SMC, and following a selective submission from the company, rivaroxaban has been accepted for restricted use in patients who have poor international normalised ratio (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.

The key evidence to support the use of edoxaban for the prevention of stroke and systemic embolism in patients with NVAF comes from one large, double-blind, randomised, phase III study (ENGAGE AF-TIMI 48). This study included 21,105 patients aged ≥21 years with documented atrial fibrillation (including paroxysmal, persistent or permanent) on electrical tracing within the previous 12 months in whom anticoagulant therapy was indicated and planned. Patients had a $CHADS_2$ score of ≥2. Patients who were receiving or had received prior anticoagulants (vitamin K antagonists [VKA]) or antiplatelets as well as those who were naïve to anticoagulant/antiplatelet treatment were eligible to enroll.

Eligible patients were randomised equally to receive edoxaban 60mg daily, edoxaban 30mg daily or warfarin with dose adjusted to achieve an INR of 2.0 to 3.0. In both edoxaban groups, the dose was

halved in patients with one or more of the following clinical factors: moderate renal impairment (creatinine clearance 30 to 50 mL/minute), low body weight (≤ 60 kg) or concomitant use of specific P-glycoprotein (P-gp) inhibitors (verapamil, quinidine, dronedarone). Randomisation was stratified by $CHADS_2$ score (2 or 3 versus 4, 5 or 6) and need for reduced edoxaban dose.

The primary outcome was the composite of stroke (ischaemic or haemorrhagic) or systemic embolism, and the primary analysis tested the non-inferiority of edoxaban with warfarin. This used a Cox proportional hazards model with the stratification factors ($CHADS_2$ score and need for reduced edoxaban dose) as variables in the modified intention to treat (mITT) population (all randomised patients who received at least one dose of study drug) during the on-treatment period. Non-inferiority was concluded if the upper boundary of the 97.5% confidence interval (CI) for the hazard ratio (HR) for edoxaban versus warfarin was ≤1.38. If non-inferiority was confirmed, tests for superiority were performed in the ITT population (all randomised patients) during the overall study period. Sequential multiplicity adjustment procedures were used in a hierarchical way to control the overall rate of type I error. Results are presented below for the licensed dose of edoxaban (60mg daily, reduced to 30mg daily in patients with one or more specified clinical factors) and warfarin only.

After a median duration of follow-up of 2.8 years, the annual rates of the composite primary endpoint were 1.18% for edoxaban and 1.50% for warfarin in the mITT population: HR 0.79 (97.5% CI: 0.63 to 0.99) p<0.001, meeting the pre-specified criteria for non-inferiority (Table 1). However, subsequent analysis of superiority, performed in the ITT population, was not met, with annual rates of a primary event of 1.57% and 1.80% respectively: HR 0.87 (97.5% CI: 0.73 to 1.04) (p=0.08).[2,3]

Sensitivity analysis, using the composite outcome of ischaemic stroke or systemic embolic event (as recommended by the European Medicines Agency [EMA]) in the per-protocol population found annual rates of 0.93% in edoxaban patients and 1.01% in warfarin patients: HR 0.92 (97.5% CI: 0.71 to 1.23), confirming non-inferiority. Subsequent sensitivity analysis of superiority (using this outcome in the ITT population) found annual rates of 1.33% and 1.36% respectively: HR 0.98 (99% CI: 0.78 to 1.23) (p=0.79).[3]

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

	ENGAGE AF-TIMI 48 study			
	Edoxaban* (n=7,035)		**Warfarin (n=7,036)**	
	Number of patients	**Annual rate**	**Number of patients**	**Annual rate**
Primary endpoint (mITT population)				
Stroke or systemic embolism	182/7,012	1.18%	232/7,012	1.50%
HR (97.5% CI) versus warfarin	0.79 (0.63 to 0.99) p≤0.0001 for non-inferiority			
Components of primary endpoint: (mITT population)				
Stroke (total)	174/7,012	1.13%	219	1.41%
HR (95% CI) versus warfarin	0.80 (0.66 to 0.98) p=0.03			
Ischaemic stroke	135/7,012	0.87%	144	0.93%
HR (95% CI) versus warfarin	0.94 (0.75 to 1.19) p=0.63			
Haemorrhagic stroke	40/7,012	0.26%	76	0.49%
HR (95% CI) versus warfarin	0.53 (0.36 to 0.78) p=0.0012			
Systemic embolism	8/7,012	0.05%	13	0.08%
HR (95% CI) versus warfarin	0.62 (0.26 to 1.50) p=0.29			

Other secondary outcomes (ITT population)				
Composite of stroke, systemic embolism or cardiovascular death	728/7,035	3.85%	831/7,036	4.43%
HR (95% CI) versus warfarin	0.87 (0.78 to 0.96) p=0.005			
Composite of myocardial infarction, stroke, systemic embolism or cardiovascular death	827/7,035	4.41%	926/7,036	4.98%
HR (95% CI) versus warfarin	0.88 (0.81 to 0.97) p=0.01			
Composite of stroke, systemic embolism or death from any cause	949/7,035	5.01%	1,046/7,036	5.57%
HR (95% CI) versus warfarin	0.90 (0.82 to 0.98) p=0.02			

* the dose of edoxaban was 60mg daily, reduced to 30mg in patients with clinical factors as per licensed indication

HR: hazard ratio, CI: confidence interval, p-values for superiority over warfarin, mITT: modified intention to treat, ITT: intention to treat

The main net clinical outcome (a composite of stroke, systemic embolism, major bleeding or death) occurred in significantly fewer edoxaban than warfarin patients (1,323/7,012 [7.26% per year] versus 1,462/7,012 warfarin patients [8.11% per year]): HR 0.89 (95% CI: 0.83 to 0.96), p=0.003.[2]

Subgroup analyses found that the treatment effect of edoxaban versus warfarin was generally consistent across the range of subgroups. However, in patients with good renal function or good control of warfarin therapy, there was a trend towards a reduced treatment effect.

Summary of evidence on comparative safety

During the ENGAGE AF-TIMI 48 study, adverse events (including bleeding) were reported in 86% (6,044/7,012) of the edoxaban group and 86% (6,068/7,012) of the warfarin group. These were considered treatment-related in 28% and 32% of patients respectively, and serious adverse events occurred in 36% and 38% of patients respectively. Adverse events led to permanent discontinuation of study drug in 15% edoxaban and 15% warfarin patients and were fatal in 4.4% and 5.2% patients respectively.[3]

The key safety outcome for an antithrombotic agent such as edoxaban is the risk of bleeding. The primary safety outcome of the study was major bleeding defined according to a modified version of the International Society on Thrombosis and Haemostasis (ISTH) criteria as clinically overt bleeding accompanied by at least one of the following: reduction in haemoglobin level of ≥2g/dL adjusted for transfusions (each transfused unit of packed red blood cells or whole blood counted as a decrease in haemoglobin of 1g/dL); 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 30 days after the last dose. As illustrated in the table below, the annual rate of major bleeding was significantly lower with edoxaban compared with warfarin. Each of the annual rates of intra-cranial bleeding, major or clinically relevant non-major bleeding and fatal bleeding were significantly lower with edoxaban than warfarin (p<0.001). However, gastrointestinal bleeding was significantly higher in the edoxaban group.[2,4]

Table 2: Results of key safety endpoints[2]

	ENGAGE AF-TMI 48 study			
	Edoxaban* (n=7,012)		Warfarin (n=7,012)	
	Number of patients	Annual rate	Number of patients	Annual rate
Major bleeding	418	2.75%	524	3.43%
HR (95% CI) versus warfarin	0.80 (0.71 to 0.91) p<0.001			
Clinically relevant non-major bleeding	1,214	8.67%	1,396	10.15%
HR (95% CI) versus warfarin	0.86 (0.79 to 0.93) p<0.001			
Intra-cranial bleeding	61	0.39%	132	0.85%
HR (95% CI) versus warfarin	0.47 (0.34 to 0.63) p<0.001			
Fatal bleeding	32	0.21%	59	0.38%
HR (95% CI) versus warfarin	0.55 (0.36 to 0.84) p=0.006			
Gastro-intestinal bleeding	232	1.51%	190	1.23%
HR (95% CI) versus warfarin	1.23 (1.02 to 1.50) p=0.03			

* the dose of edoxaban was 60mg daily, reduced to 30mg in patients with clinical factors as per licensed indication

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

During the study, adverse events (excluding bleeding) were reported in 84% (5,911/7,012) of the edoxaban group and 84% (5,910/7,012) of the warfarin group. These were considered treatment-related in 11% (778/7,012) and 12% (861/7,012) of patients respectively. The rates of hepatic events, neoplasms and bone fractures were similar in each group.[2]

Summary of clinical effectiveness issues

Edoxaban is the third oral direct factor Xa inhibitor to be licensed to prevent stroke and systemic embolism in adult patients with NVAF and at least one risk factor. The other direct oral anticoagulants, dabigatran, rivaroxaban and apixaban, are also licensed for this indication and have been accepted for use or restricted use by SMC. Current guidance recommends the use of the direct oral anticoagulant agents as an alternative to warfarin.

In the pivotal ENGAGE AF-TIMI 48 study, edoxaban (at the licensed dose of 60mg daily, reduced to 30mg when indicated) was found to be non-inferior to warfarin in the primary analysis but not superior to warfarin. The results were presented as annual incidence rates and absolute differences between treatment groups were small: 0.32% between edoxaban and warfarin for the primary outcome, equivalent to a 21% relative risk reduction. The difference between the groups in this composite outcome was mainly driven by a reduction in the rate of stroke. Since patients with atrial fibrillation have a higher risk of disabling and recurrent stroke and mortality from stroke than from those related to other causes, reductions in stroke rate are clinically important. However, the difference was most evident in the incidence of haemorrhagic stroke. The EMA currently recommends that the primary efficacy outcome excludes haemorrhagic strokes, which should be assessed as a safety outcome, and sensitivity analysis excluding this confirmed non-inferiority.[3]

Study patients had a $CHADS_2$ score of ≥2 (mean of 2.8), while patients eligible for treatment with edoxaban under the marketing authorisation would have one or more risk factors which could include patients with a $CHADS_2$ score of 1. Based on an extrapolated benefit in lower risk patients, the EMA agreed that edoxaban may provide additional benefit versus no treatment in patients with a $CHADS_2$ score of 1 and that this has been accepted for similar agents. Although the study used the $CHADS_2$

score to assess patients' level of risk, current guidelines recommend using the CHA_2DS_2-VASc score which may more accurately calculate the stroke risk.

Subgroup analysis suggested that the treatment effect of edoxaban over warfarin was less, and favoured warfarin, in patients with good renal function (creatinine clearance ≥80mL/min). The SPC notes that a trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared with well-managed warfarin. Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk. It also recommends that renal function should be monitored at the beginning of treatment in all patients and afterwards when clinically indicated.[1] Study patients in the warfarin group had a median of 68% time in therapeutic range (INR 2.0 to 3.0). However, subgroup analysis also indicated that the treatment effect of edoxaban versus warfarin may also be less in patients who have good INR control, and favoured warfarin in patients with the best control (quartile with >73.9% of INR values in the therapeutic range).[1,3]

There are no direct comparative data for edoxaban versus the other direct oral anticoagulants. The submitting company presented a network meta-analysis (NMA) to compare the efficacy and safety of edoxaban with apixaban, dabigatran and rivaroxaban in patients with NVAF and a $CHADS_2$ score ≥2. The analysis used mixed Poisson regression with random effects and warfarin as a common comparator. The network included four studies. Since two studies included patients with a $CHADS_2$ score ≥1, the primary analysis used the subgroup of patients from these studies with $CHADS_2$ score ≥2. The results of several efficacy and safety outcomes were assessed but the main outcomes were the composite of stroke/systemic embolism and major bleeding. Results presented as risk ratios (95% CI) suggested that there was no significant difference between edoxaban and apixaban, dabigatran or rivaroxaban for stroke/systemic embolism. The risk of major bleeding with edoxaban was similar to apixaban but significantly less than dabigatran and rivaroxaban. Sensitivity analysis was performed in all study patients including those with a $CHADS_2$ score of 1. There were a number of differences between the studies in terms of the relative risk of stroke, duration of follow-up and time in the therapeutic range for warfarin-treated patients. However, despite these limitations, edoxaban was considered to be similar to the other direct oral anticoagulants.

There is no specific antidote to edoxaban and, since it acts at a different step in the coagulation cascade from warfarin, the standard strategies used to reverse warfarin are not appropriate. Edoxaban dose interruption or discontinuation and symptomatic treatment are initially recommended in patients who bleed. This may also be an issue in patients who require emergency surgery. The SPC advises that edoxaban should be stopped at least 24 hours before surgical or other procedures.[1] For life-threatening bleeding that cannot be controlled with transfusion or haemostasis, the administration of a 4-factor prothrombin complex concentrate has been shown to reverse the effects of edoxaban 30 minutes after completing the infusion.[1]

The introduction of edoxaban would offer another alternative new anticoagulant to dabigatran, rivaroxaban and apixaban. 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. Edoxaban, like dabigatran, rivaroxaban and 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. Edoxaban, like rivaroxaban, is administered once daily; while dabigatran and apixaban are administered twice daily.[5,6,7]

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis which compared edoxaban against warfarin, rivaroxaban, dabigatran 110mg, dabigatran 150mg and apixaban in the licensed population. SMC clinical experts have confirmed that the comparators are appropriate.

The company used a Markov cohort model to assess the cost-effectiveness of edoxaban against the comparators. The model consisted of 18 health states and the analysis used a time horizon of 30 years. In terms of model structure, all patients start in the stable atrial fibrillation health state and patients could move to myocardial infarction, systemic embolism, ischemic stroke, or haemorrhagic stroke health states. Also, other intracranial haemorrhage (other ICH), TIA, non-ICH major bleed and clinically relevant non-major bleeds were included in the model as events where costs and disutilities were applied for the duration of the event. Patients could die throughout the model.

The main sources of clinical data used in the analysis were the ENGAGE AF-TIMI 48 study and the NMA described above. The ENGAGE AF-TIMI 48 study was used to generate estimates for edoxaban in relation to key clinical variables..The NMA provided hazard ratios for dabigatran, rivaroxaban, apixaban and warfarin versus edoxaban. The network was informed by the pivotal phase III study for each comparator: apixaban (ARISTOTLE), dabigatran (RE-LY), rivaroxaban (ROCKET-AF).

Baseline utilities were taken from the ENGAGE AF-TIMI study. Utilities were adjusted due to patients transitioning to health states other than stable disease or experiencing an event and the values were derived from the published literature or other health technology assessments. The analysis also included a disutility to capture a decline in utility as the patient ages.

Medicines costs were included in the analysis, as were the costs associated with monitoring of warfarin. The analysis assumed patients required 18 monitoring visits per year. The cost of managing and treating the disease including complications, adverse events and death were also included in the economic model.

The base case results indicated that edoxaban was dominant (i.e. was more effective and also less costly) versus rivaroxaban with estimated savings of £545 and a QALY gain of 0.001. The incremental cost effectiveness ratio (ICER) versus warfarin was £23,539 per quality adjusted life year (QALY) gained. This result was based on an incremental cost of £2,434 and a QALY gain of 0.103 for edoxaban versus warfarin. Edoxaban had equal QALYs to apixaban but was less expensive (£259 savings) while edoxaban was less effective and less costly than dabigatran 110mg and dabigatran 150mg respectively, with estimated savings of £38 and £78 and a QALY loss of 0.044 and 0.049.

The company provided one-way deterministic sensitivity analyses for edoxaban versus warfarin, rivaroxaban, apixaban, dabigatran 110mg and dabigatran 150mg respectively. For comparisons against warfarin, the analysis was most sensitive to increasing the acute mortality of non-ICH major bleed (£83,478), increasing the starting age to 89 (£56,035), including a monitoring cost for edoxaban (£45,838), increasing the medicines cost of edoxaban (£36,994) and reducing the monitoring cost for warfarin (£26,480).

For comparisons against rivaroxaban, apixaban, dabigatran 110mg and dabigatran 150mg, the company primarily presented results in terms of Net Monetary Benefits (NMB). When the cost of edoxaban was increased and monitoring was introduced for edoxaban, NMB were negative for comparisons against all comparators. Reducing the starting age of the model also generated negative

NMB for edoxaban versus dabigatran 110mg and dabigatran 150mg respectively. Increasing the acute mortality of non-ICH major bleed for comparisons against rivaroxaban and apixaban again generated negative NMB. Negative NMB results indicate edoxaban is not cost-effective in these scenarios. Finally, when acute mortality associated with major bleeding and the rate of other cause discontinuation per month for rivaroxaban was increased, the ICER increased to £10,079 and £20,669 respectively versus rivaroxaban.

The main weaknesses were:

- Incremental analysis provided by the company which included edoxaban, warfarin, rivaroxaban, apixaban, dabigatran 150mg and dabigatran 110mg as comparators, identified that edoxaban was extendedly dominated by both dabigatran regimens (i.e. the ICER for edoxaban is higher than that of the next more effective alternative and therefore should be excluded from the incremental analysis). The incremental analysis also identified that dabigatran 150mg was the cost effective treatment option and not edoxaban when all treatment options were considered. The company noted that edoxaban was not the most cost-effective option on an incremental basis; however, it suggested that edoxaban was cost-effective on a pairwise basis versus the most commonly used agents in Scotland, namely warfarin and rivaroxaban. Following discussions, the Committee considered that the primary comparators included rivaroxaban and apixaban which edoxaban either dominated, or was as effective and less costly.
- There were a number of weaknesses regarding the NMA in terms of how it was used to support the economic evaluation. The company had assumed that if no data were available for a particular outcome from the NMA a hazard ratio of 1 was used in the analysis. This assumption potentially favoured edoxaban versus some comparators due to the lower intervention costs estimated by the economic model. The analysis had assumed that the efficacy of the medicines in relation to each other remained constant throughout the analysis. However, the SMC Statistical Advisor reported that the data suggested differences in efficacy between the medicines may not remain constant over time. The company also reported that although the pivotal study did not include patients with a $CHADS_2$ score of 1, the study population was still generalisable to the licensed indication. However, in the economic analysis the company chose to restrict the comparator populations to patients with a $CHADS_2$ score of ≥ 2 when possible instead of using the whole study population. On balance, the NMA and its use in the economics was considered sufficiently robust to inform estimates of comparative efficacy regarding the comparators in the economic evaluation.
- The analysis did not include monitoring costs for edoxaban, rivaroxaban, apixaban, dabigatran 110mg or dabigatran 150mg; however, patients treated with these medicines may receive renal function monitoring. The company provided a sensitivity analysis which included renal function monitoring and the ICER for edoxaban versus warfarin was £25,853. Edoxaban also dominated rivaroxaban, was equally effective and less expensive than apixaban, and was less effective and less costly than both dabigatran regimens in this scenario.

Despite these issues, the economic case has been demonstrated

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from AntiCoagulation Europe (ACE) and Thrombosis UK, which are both registered charities.

- Both AntiCoagulation Europe and Thrombosis UK have received pharmaceutical company

funding in the past two years, but neither has received any from the submitting company.

- Atrial Fibrillation (AF) describes a heart rhythm disturbance which can cause a person to experience a highly irregular pulse rate. Symptoms can include palpitations (thumping heart) dizziness, chest pains and breathlessness. When experiencing an episode, it can cause anxiety and distress to the person or carer. Patients with atrial fibrillation have to take anticoagulants to prevent stroke and systemic emboli. If stroke and/or embolism is not prevented in these patients it can have life-changing consequences and even lead to premature death.

- Many patients are on warfarin which needs to be dose adjusted dependent on the INR blood levels which require regular monitoring. It also interacts with many foods and medicines.

- Edoxaban would provide patients with another oral anticoagulation option which may impact positively on their day to day, social and working lives as it is a once daily dose and does not require any regular monitoring. In addition, it does not need significant adjustments to diet and lifestyle.

Additional information: guidelines and protocols

SIGN updated guideline number 129 "Antithrombotics: indications and management. A national clinical guideline" in June 2013.[8] 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, rivaroxaban or apixaban can be considered as alternatives to warfarin in the management of patients with atrial fibrillation with one or more risk factor for stroke. However consideration should be given to the relative lack of experience of long term use compared with a vitamin K antagonist or aspirin; the lack of a licensed product for rapid reversal of the anticoagulant effect and the limited data on use in patients at the extremes of body weight and those with hepatic impairment. Antiplatelet therapy should only be considered where warfarin or one of the alternative new anticoagulants has been declined. This guideline predates the availability of edoxaban.

In June 2014, NICE published clinical guideline (CG) 180 "Atrial fibrillation: The management of atrial fibrillation".[9] It recommends that stroke risk should be assessed in patients with paroxysmal, persistent or permanent AF, using the CHA_2DS_2-VASc stroke risk score. Anticoagulation should be offered to people with a CHA_2DS_2-VASc score ≥2, taking bleeding risk into account. Anticoagulation should be considered in men with a CHA_2DS_2-VASc score of 1, taking bleeding risk into account. Apixaban, dabigatran, rivaroxaban and vitamin K antagonist are each recommended as options for anticoagulation. Stroke prevention therapy should not be offered to people aged <65 years with AF and no risk factors other than their sex (ie CHA_2DS_2-VASc score of 0 for men and 1 for women). This guideline predates the availability of edoxaban.

The European Society of Cardiology (ESC) published "2012 focused update of the ESC guidelines for the management of atrial fibrillation" in 2012.[10] 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 antithrobotic therapy (VKA, newer oral anticoagulant therapy, aspirin/clopidogrel or aspirin).

Healthcare Improvement Scotland published a consensus statement "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation" in April 2012.[11] 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*". In May 2015, Healthcare Improvement Scotland issued a statement to reflect the availability at that time of three novel oral anticoagulants (NOACs) for use in NHSScotland (dabigatran, rivaroxaban and apixaban), each with different efficacy and safety profiles. The 2012 statement was not refreshed but remains as an information source for use by services developing local prescribing policies to agree choice and use of NOACs.

Additional information: comparators

Warfarin, dabigatran, rivaroxaban and apixaban.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Edoxaban	**30mg or 60mg orally daily**	**764**
Dabigatran	110mg or 150mg orally twice daily	800
Apixaban	2.5mg or 5mg orally twice daily	800
Rivaroxaban	15mg or 20mg orally daily	764
Warfarin	Orally as determined by prothrombin time	12 to 39

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 August 2015, except edoxaban which is from eMIMs 3 August 2015.

Additional information: budget impact

The company estimated that 10,862 patients in year 1 would be eligible for treatment, rising to 25,066 patients in year 5. The market share estimated by the company was 0.92% in year 1, rising to 12.55% in year 5. When market share was taken into account, the company estimated 99 patients would be treated in year 1, rising to 3,145 in year 5.

The company estimated the gross medicines budget impact to be £75k in year 1, rising to £2.2m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated as savings of £3k in year 1, rising to £106k in year 5.

References

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

1. Daiichi Sankyo UK Limited. Edoxaban film-coated tablets (Lixiana®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated July 2015.

2. Giugliano RP, Ruff CT, Braunwald E et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369:2093-104.

3 European Medicines Agency. European public assessment report for edoxaban (Lixiana). EMA/321083/2015 23 April 2015.

4. Ruff CT, Giugliano RP, Antman EM et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: Design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF–TIMI 48). Am J Med 2010;160:635-41.

5. Bayer plc. Rivaroxaban film-coated tablets (Xarelto®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated July 2015.

6. Bristol-Myers Squibb-Pfizer. Apixaban film-coated tablets (Eliquis®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated July 2014.

7. Boehringer Ingelheim Limited. Dabigatran hard capsules (Pradaxa®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated December 2014.

8. Scottish Intercollegiate Guidelines Network (SIGN) 129. Antithrombotics: indications and management. A national clinical guideline. Updated June 2013.

9. The National Institute for Health and Clinical Excellence. Clinical guideline 180: The management of atrial fibrillation. June 2014.

10. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). 2012 focused update of the ESC guidelines for the management of atrial fibrillation. Eur Heart J 2012 doi:10.1093/eurheartj/ehs253

11. Healthcare Improvement Scotland. Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation - consensus statement. April 2012. www.healthcareimprovementscotland.org

This assessment is based on data submitted by the applicant company up to and including 11 September, 2015.

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.