

dabigatran etexilate 110mg and 150mg hard capsules (Pradaxa®) SMC No. (672/11)

Boehringer Ingelheim Ltd

05 August 2011

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

dabigatran etexilate (Pradaxa®) 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 with one or more of the following risk factors:

- previous stroke, transient ischaemic attack, or systemic embolism
- left ventricular ejection fraction <40%
- symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2
- age ≥75 years
- age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension

Dabigatran etexilate was at least as effective as standard oral anticoagulation at preventing stroke or systemic embolism in one large, open-label study in patients with atrial fibrillation and at least one risk factor for stroke. This was not associated with an increased risk of major bleeding.

The economics case made supports the use of the proposed sequenced dosing regimen (whereby the dose is reduced from 150mg twice daily to 110mg twice daily in patients aged ≥ 80 years). This applies whether the alternative treatment is warfarin, aspirin or 'no treatment' (i.e. neither warfarin nor aspirin).

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Published 12 September 2011

Indication

For the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more of the following risk factors:

- previous stroke, transient ischaemic attack, or systemic embolism
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- symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2
- age ≥ 75 years
- age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension

Dosing Information

150mg twice daily. Patients aged between 75 to 80 years should be treated with 150mg twice daily. A dose of 110mg twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high. Patients aged ≥ 80 years should be treated with 110mg twice daily due to the increased risk of bleeding in this population. For patients at high risk of bleeding the lower dose may be recommended – refer to the SPC for details.

Therapy should be continued long term.

Product availability date

August 2011

Summary of evidence on comparative efficacy

Dabigatran etexilate is a prodrug hydrolysed in the plasma and liver to the active substance dabigatran. It is an oral, competitive, reversible direct thrombin inhibitor which inhibits free and fibrin-bound thrombin and thrombin-induced platelet aggregation. Dabigatran was originally licensed for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. This submission focuses on the new indication, the prevention of stroke and systemic embolism in adult patients with atrial fibrillation.

One pivotal phase III, multi-centre, randomised study compared two blinded doses of dabigatran etexilate (hereafter referred to as dabigatran) with open-label warfarin. Eligible patients (n=18,113) had non-valvular atrial fibrillation and at least one additional risk for stroke from: history of stroke, transient ischaemic attack (TIA) or systemic embolism; left ventricular ejection fraction <40%; symptomatic heart failure; age ≥75 years or age ≥65 years and one of the following: diabetes mellitus on treatment, documented coronary artery disease or hypertension requiring medical treatment. Balanced proportions of vitamin K antagonist (VKA) naïve (previously received ≤2 months of VKA therapy) and VKA-experienced patients were enrolled. Patients were randomised to receive dabigatran 110mg (n=6,015) or 150mg (n=6,076) twice daily or warfarin (n=6,022) adjusted to maintain an international normalised ratio (INR) of 2.0 to

3.0. During the study, concomitant therapy with aspirin (<100mg daily) or other antiplatelet agents was permitted.

The primary outcome was the composite of stroke or systemic embolism. The study primarily assessed the non-inferiority of each dose of dabigatran with warfarin using a non-inferiority margin of 1.46 for the upper bound of the one-sided confidence interval (CI) for the relative risk of an outcome. If non-inferiority was confirmed, tests for superiority were performed. After the database was locked, several additional primary efficacy and safety outcome events were discovered. This led to a re-analysis of a re-evaluated database and identification of 81 new clinical events in 80 patients plus 28 cases of silent myocardial infarction (MI). The results of this re-analysis are presented below.

After a median duration of follow-up of 2 years, the annual rates of the composite primary endpoint were 1.54%, 1.11% and 1.71% for dabigatran 110mg, 150mg and warfarin respectively. Both dabigatran groups met the pre-specified criteria for non-inferiority versus warfarin and the dabigatran 150mg group demonstrated superiority over warfarin. Details are given in the table below.

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

	Dabigatran 110mg (n=6015)		Dabigatran 150mg (n=6076)		Warfarin (n=6022)	
	No. of patients	Annual rate	No. of patients	Annual rate	No. of patients	Annual rate
Primary endpoint:						
Stroke/ systemic embolism	183	1.54%	134	1.11%	202	1.71%
HR (95% CI) vs warfarin	0.90 (0.74 to 1.10) p=0.29		0.65 (0.52 to 0.81) p≤0.001			
Components of primary endpoint:						
Stroke (total)	171	1.44%	122	1.01%	186	1.58%
HR (95% CI) vs warfarin	0.91 (0.74 to 1.12) p=0.38		0.64 (0.51 to 0.81) p<0.001			
Ischaemic or unspecified stroke	159	1.34%	111	0.92%	143	1.21%
HR (95% CI) vs warfarin	1.11 (0.88 to 1.39) p=0.35		0.76 (0.59 to 0.97) p=0.03			
Haemorrhagic stroke	14	0.12%	12	0.10%	45	0.38%
HR (95% CI) vs warfarin	0.31 (0.17 to 0.56) p<0.001		0.26 (0.14 to 0.49) p<0.001			
Systemic embolism	15	0.13%	13	0.11%	21	0.18%
HR (95% CI) vs warfarin	0.71 (0.37 to 1.38) p=0.31		0.61 (0.30 to 1.21) p=0.16			
Other endpoints						
Death from vascular causes	289	2.43%	274	2.28%	317	2.69%
HR (95% CI) vs warfarin	0.90 (0.77 to 1.06) p=0.21		0.85 (0.72 to 0.99) p=0.04			

Death from any cause	446	3.75%	438	3.64%	487	4.13%
HR (95% CI) vs warfarin	0.91 (0.80 to 1.03) p=0.13		0.88 (0.77 to 1.00) p=0.052			
Net clinical benefit	873	7.34%	855	7.11%	933	7.91%
HR (95% CI) vs warfarin	0.92 (0.84 to 1.01) p=0.09		0.90 (0.82 to 0.99) p=0.02			

HR: hazard ratio, CI: confidence interval, vs: versus, N/A: not available, p-values for superiority over warfarin

The difference between the groups in the composite primary endpoint was mainly driven by a reduction in the rate of stroke. Compared to warfarin, dabigatran 150mg significantly reduced the rate of all types of stroke including haemorrhagic, ischaemic or unspecified as well as those categorised as non-disabling or disabling/fatal.

The annual rate of MI (including silent MI) was numerically higher with dabigatran 110mg and 150mg (0.82% and 0.81% respectively) compared with warfarin (0.64%). Death from vascular causes was reported at annual rates of 2.43%, 2.28% and 2.69% and death from any cause of 3.75%, 3.64% and 4.13% in dabigatran 110mg, 150mg and warfarin treated patients respectively. The difference between dabigatran 150mg and warfarin bordered on statistical significance for any deaths and reached statistical significance for vascular death.

Net clinical benefit was a composite of stroke, systemic embolism, pulmonary embolism, acute MI, death from any cause and major bleeds for which annual rates of 7.34%, 7.11% and 7.91% were reported for dabigatran 110mg, 150mg and warfarin respectively. The difference reached statistical significance between dabigatran 150mg and warfarin.

The treatment effect of dabigatran was similar across the various subgroup analyses, including VKA experience, creatinine clearance and CHADS₂ score.

Summary of evidence on comparative safety

The key safety outcome for an antithrombotic agent, like dabigatran, is the risk of bleeding. Major bleeding was defined as at least one of the following: associated with reduction in haemoglobin level of $\geq 20\text{g/L}$; 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. Major bleeding was defined as life-threatening if at least one of the following was met: fatal, symptomatic intracranial bleed; reduction in haemoglobin level of $\geq 50\text{g/L}$; transfusion of ≥ 4 units of blood or packed cells; associated with hypotension requiring the use of intravenous inotropic agents or necessitating surgical intervention.

As illustrated in the table below, the annual rate of major bleeding was numerically lower in the dabigatran groups compared with warfarin and the difference was statistically significant between dabigatran 110mg and warfarin. Each of the annual rates of life-threatening bleeding, minor bleeding, major plus minor bleeding and intra-cranial bleeding were significantly lower with both doses of dabigatran than with warfarin ($p < 0.05$). The annual rate of gastro-intestinal bleeding was numerically higher in both dabigatran groups compared to warfarin and the difference reached statistical significance with the 150mg group ($p = 0.001$).

Table 2: Results of key safety endpoints

	Dabigatran 110mg (n=6015)		Dabigatran 150mg (n=6076)		Warfarin (n=6022)	
	No. of patients	Annual rate	No. of patients	Annual rate	No. of patients	Annual rate
Any major bleeding	342	2.87%	399	3.32%	421	3.57%
HR (95% CI) versus warfarin	0.80 (0.70 to 0.93) p=0.003		0.93 (0.81 to 1.07) P=0.31			
Life-threatening bleeding	147	1.24%	179	1.49%	218	1.85%
HR (95% CI) versus warfarin	0.67 (0.54 to 0.82) p<0.001		0.80 (0.66 to 0.98) P=0.03			
Gastro-intestinal bleeding	137	1.15%	188	1.56%	126	1.07%
HR (95% CI) versus warfarin	1.08 (0.85 to 1.38) p=0.52		1.48 (1.18 to 1.85) p=0.001			
Intra-cranial bleeding	27	0.23%	38	0.32%	90	0.76%
HR (95% CI) versus warfarin	0.30 (0.19 to 0.45) p<0.001		0.41 (0.28 to 0.60) p<0.001			

HR: hazard ratio; CI: confidence interval

The relative risk of major bleeding increased with age for dabigatran compared to warfarin and was highest in patients aged over 80 years. In patients aged ≥ 75 years, the hazard ratio for major bleeding was 1.01 (95% CI: 0.83 to 1.23) with dabigatran 110mg versus warfarin and 1.18 (0.98 to 1.43) with dabigatran 150mg versus warfarin. In patients aged ≥ 80 years, the hazard ratios were 1.12 (95% CI: 0.84 to 1.49) and 1.35 (1.03 to 1.77) respectively.

In terms of non-bleeding adverse events, dyspepsia (including upper abdominal pain, abdominal pain, abdominal discomfort and dyspepsia) was the only adverse event to be reported significantly more frequently in the dabigatran groups (110mg: 12% and 150mg: 11%) compared to the warfarin group (5.8%) ($p<0.001$). Gastro-intestinal symptoms (including pain, vomiting and diarrhoea) that led to discontinuation were reported in numerically more dabigatran (110mg and 150mg) than warfarin patients (2.2% and 2.1% versus 0.6%). This and the increased rate of gastro-intestinal bleeding may be partly due to the acidity of the tartaric acid core in the dabigatran capsules.

Significantly more patients in the dabigatran groups (2.7% in each dosage group) discontinued study medication because of serious adverse events than in the warfarin group (1.7%) ($p<0.001$).

The frequency of liver function test (alanine and aspartate aminotransferase) results reaching three times the upper limit of normal was similar in dabigatran and warfarin groups (1.9 to 2.2%). The proportions of patients requiring hospitalisation for hepatobiliary disorders were low and similar in all three treatment groups.

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. Both dabigatran doses were non-inferior to warfarin and the 150mg dose was found to be superior, although the absolute difference was small (0.6%). The difference between groups in the composite endpoint was mainly due to the reduction in stroke. Dabigatran 150mg significantly reduced the annual rates of all types of stroke compared to warfarin, including disabling/fatal strokes. This is clinically relevant 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.

The main limitation of the study was its open-label design which could have introduced bias in reporting or adjudication of events. However this was minimised by requiring blinded evaluation by two independent investigators for all outcomes and the use of objective outcomes. Discontinuation rates were reported as 14.5%, 15.5% and 10.2% with dabigatran 110mg, dabigatran 150mg and warfarin respectively after 1 year and 20.7%, 21.2% and 16.6% respectively after 2 years.

The study excluded patients who had a recent stroke or were at high risk of bleeding. During the pivotal study, the INR was within the therapeutic range for, on average, 64% 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 study outcomes for the three treatment groups 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 dabigatran compared to warfarin diminished with improving INR control. For the higher two quartiles of time in the therapeutic range, the hazard ratio of net clinical benefit moved to numerically favouring warfarin over dabigatran. However the baseline characteristics of the quartile subgroups were not well matched. There appeared to be no relationship between INR control and intracranial bleeding.

Concomitant use of aspirin (<100mg daily) or other antiplatelet agents was permitted during the study. At baseline, 40%, 39% and 41% of dabigatran 110mg, dabigatran 150mg and warfarin patients respectively were receiving concomitant aspirin and it was used continuously during the treatment period in 21%, 20% and 21% of patients respectively. This increased the risk of bleeding in these patients.

During the pivotal study, dabigatran was associated with an increased risk of dyspepsia and gastro-intestinal bleeding compared to warfarin. It is suggested that these effects may be due to acidity from the tartaric acid core of the capsules and may have contributed to higher discontinuation rates in the dabigatran groups. It is unclear how dabigatran would affect patients susceptible to gastro-intestinal adverse events in clinical practice. There was also a numerically higher incidence of MI in the dabigatran groups and it is unclear whether this is due to a loss of the protective effect of warfarin or whether thrombin inhibition contributed to this. Although there was no difference between dabigatran and warfarin in terms of effects on liver function during the pivotal study, longer term data are required.

There is no specific antidote to dabigatran and since it acts at a different step in the coagulation cascade from warfarin, the standard strategies used to reverse warfarin are not appropriate.

However, the anticoagulant effects of dabigatran are shorter than warfarin and since dabigatran elimination is mainly via the kidneys, it is dependent on renal function. Dabigatran discontinuation and supportive measures are initially recommended in patients who bleed. This may also be an issue in patients who require emergency surgery. The Summary of Product Characteristics advises that temporary discontinuation of dabigatran may be required in patients undergoing surgery or invasive procedures and includes a table of discontinuation rules.

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. Dabigatran 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. Although dabigatran is associated with fewer interactions than warfarin, co-administration with verapamil requires dabigatran dose reduction from 150mg to 110mg twice daily.

Experts consulted by SMC indicated that there are patients who are unsuitable for warfarin but who would benefit from anticoagulation therapy.

An indirect comparison in the form of a mixed treatment comparison was presented to allow comparison with aspirin, as a secondary analysis. The primary analysis in the economics case uses warfarin as a comparator and is based on the results of the pivotal study described above.

Healthcare Improvement Scotland has facilitated a consensus meeting to be held following the publication of SMC detailed advice on dabigatran that will provide a forum for clinicians, managers and patients to discuss the safe and effective use of this medicine. It is proposed that a national consensus statement will be the key output from this meeting.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis in the form of a Markov model allowing various comparisons to be made. The modeled treatment strategy most closely resembling the licensed dose was dabigatran 150mg twice daily for patients under the age of 80, with the patient being switched to 110mg twice daily when they reach the age of 80. This was also referred to as the sequence option by the submitting company because the high-dose and low-dose were used in sequence, as distinct from the single dose used in the main clinical study.

The main comparator was warfarin plus INR monitoring with the aim of maintaining INR in a target range of 2.0 to 3.0.

Other potential dabigatran regimens included 150mg twice daily and 110mg twice daily dosing, reflecting the main clinical study, and 110mg twice daily started after the age of 80. A comparison with aspirin was also included and a comparison with 'no treatment' was supplied on request by the submitting company.

The model was used to estimate costs and benefits over the lifetime of a cohort of patients reflecting the baseline characteristics of the main clinical study (e.g. mean age of 69). Patients

were at risk of the following events: ischaemic stroke, intracranial haemorrhage, haemorrhagic stroke, acute myocardial infarction, systemic embolism, transient ischaemic attack, extracranial haemorrhage, and minor bleed. The consequences of each type of event were modeled in terms of costs and quality adjusted life years (QALYs) using data from a variety of sources, including published studies and specifically commissioned estimates.

The main data source for effectiveness estimates was the clinical study and included two elements:

- The number of patients experiencing an event while on warfarin treatment.
- A relative risk reduction (or increase) for each type of event for dabigatran. This treatment effect was assumed to continue so long as the patient remained on treatment. Rates for aspirin were taken from a mixed treatment comparison.

Discontinuation rates on treatment were modeled from the main clinical study using a Weibull function. Discontinuing treatment was assumed to involve one GP visit and patients could switch to a second-line treatment, generally aspirin, although the model also allowed aspirin-plus-clopidogrel as an option.

Costs of monitoring INR levels while on warfarin treatment were included based on the primary care costs estimated for a 2006 NICE guideline on atrial fibrillation. On this basis, the submitting company assumed a saving of £415 per year for every patient switched from warfarin to dabigatran.

Patients started treatment with a utility value of 0.81, reflecting their diagnosis of atrial fibrillation. Utility decreased as a result of suffering events with utility values taken from various published sources. The health consequences of each type of event were considered separately, including drawing on other clinical studies. Utilities were taken from published studies. The conservative assumption was made that there was no utility loss to patients as a result of being on warfarin despite the need for regular INR testing.

In terms of costs of treating events such as stroke and bleeding, the main focus was on costs borne by the NHS, but social work costs of managing patients with a disability following stroke or intracranial haemorrhage were also considered. Costs for events were taken from various published sources with the Scottish National Tariff used where a figure was available. This was supplemented by a study of the costs of care for stroke patients in Oxfordshire and English NHS Reference Costs.

The base-case results in the submission were that dabigatran used in the sequence (150mg twice daily to age 80 and 110mg twice daily after) had an incremental cost per QALY of £6,986 compared to warfarin, based on an added cost of £1,737 and 0.25 extra QALYs. Against the other potential comparators the results were as follows:

- Versus aspirin £5,785 per QALY
- Versus 'no treatment' £1,542 per QALY

Considering the results of the model in terms of events, when 10,000 patients were treated with dabigatran in the sequence regimen instead of warfarin, the results over the lifetime of the cohort would be:

- 186 fewer ischaemic strokes (of which 52 fewer would have left the patient totally dependent but 3 more would have been fatal)

- 563 fewer intracranial haemorrhages or haemorrhagic strokes (of which 179 fewer would have left the patient totally dependent and 294 fewer would have been fatal)
- 397 more extracranial haemorrhages (of which 5 would be fatal)
- 241 more acute myocardial infarctions (of which 3 would be fatal)

Adding together deaths and major disabling events, the net effect of dabigatran use rather than warfarin use was predicted to be a reduction of 514 fatal or major disabling events (525 prevented, 11 caused). Thus 19 patients have to be commenced on the dabigatran sequence rather than warfarin to avoid one additional death or major disabling event.

There were several issues with the base-case analysis.

First, the economic model included effectiveness estimates for dabigatran in terms of changes in relative risk where the 95% confidence interval overlapped with 1.0. When these were excluded, the cost per QALY versus warfarin rose to £12,612 and versus aspirin to £8,353. However, while accepting these differences do not meet the conventional 5% limit, they should be viewed in the context of the set of circumstances in this particular example (the importance of the relative risk change, the clinical study not being powered to detect differences in this variable, and the relative risk for ischaemic stroke in the main clinical study having achieved statistical significance (0.76 with 95% confidence interval 0.59 to 0.97)).

Second, the estimate of INR monitoring savings was £415 per patient prescribed dabigatran rather than warfarin per annum. It is important to note that this is likely to be a saving in terms of staff time and laboratory capacity freed up, and would only be converted into cash savings in notable amounts if the number of staff employed fell as a result. Alternative assumptions provided by SMC clinical experts surrounding this aspect of the analysis and alternative cost figures suggested that a value of £200 per patient may have been more appropriate. Using this figure resulted in a cost per QALY of £13,347 in the comparison with warfarin when dabigatran was used in sequence.

The degree of INR control while on warfarin influences the relative cost-effectiveness of dabigatran and the manufacturer's base-case used the average from the main clinical study of 64%. However, the figure for the UK centres in the study was higher than this (72%) and, combined with the reporting of the clinical study in *The Lancet* in terms of INR quartiles, this raised a concern that dabigatran may be cost-effective only in patients with poor INR control. However, it is not clear that INR control in practice could achieve the levels in the clinical study where selected centres recruited selected patients. There are few reliable figures on time in therapeutic range in Scotland. In general, good INR control diminishes the incremental benefit of dabigatran. The submitting company provided helpful threshold analysis to show the levels of INR control at which the additional cost per QALY for dabigatran equals £30k and £20k. These values were 98% and 92% respectively.

The Summary of Product Characteristics allows the use of dabigatran at a dose of 110mg twice daily in certain circumstances. In general the cost per QALY figures for this dose are below the limits usually regarded as acceptable when compared to warfarin, aspirin or 'no treatment'. However, the cost per QALY is higher than for the sequence regimen described above.

	110mg twice daily all ages	110mg twice daily in age over 80	Sequence (150mg twice daily to age 80, then 110mg twice daily)
Warfarin	£18,177	£9,624	£6,986
Warfarin with INR savings £200 per patient	£27,260	£18,885	£13,347
Aspirin	£11,770	£4,366	£5,785
No treatment	£3,932	Lower cost, more QALYs (dominant)	£1,542

The economic evidence for the 110mg dose is acceptable when used as part of the sequence (with switch of dose at age 80) and for patients over 80. In other circumstances the sequence regimen may offer better value for money. Note that this evidence applies at the population level and decisions about individual patients also need to take account of factors such as bleeding risk and stroke risk.

Despite challenging the base-case estimates in terms of the statistical significance of changes in clinical endpoints and the value of the time released through reduced INR monitoring, the cost per QALY for dabigatran remains within normally accepted limits. There are several ways in which the estimates could be seen as being conservative. For example, no utility loss was assumed for patients being prescribed warfarin, despite lifestyle restrictions and the need to attend for monitoring. The comparison was also with warfarin control in the trial, which may exceed levels achieved in practice.

In summary, the economic case made supports the use of the proposed sequence posology. This applies whether the alternative treatment is warfarin, aspirin or 'no treatment' (i.e. neither warfarin nor aspirin). In individual cases the cost-effectiveness of dabigatran is likely to be influenced by quality of INR control while on warfarin, prognostic factors such as CHADS₂, and individually-assessed bleeding risk.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

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 (≥ 75 years). 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 $\geq$ 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 ≥ 75 years 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 ≥ 65 years 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 is expected to be reviewed in August 2011.

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.

Additional information: comparators

Comparators will depend on stroke risk assessment and will include warfarin and aspirin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Dabigatran	110 or 150mg orally twice daily	917
Warfarin	Orally as determined by prothrombin time	3 to 14
Aspirin	75 to 300mg orally daily	4 to 22

Doses are for general comparison and do not imply therapeutic equivalence. Costs for dabigatran are taken from the company submission. Costs for warfarin and aspirin are from eVadis on 2 June 2011.

Additional information: budget impact

The manufacturer estimated that around 75,000 patients in Scotland have AF. The submitting company made assumptions regarding eligibility and market share that should be regarded as commercial in confidence.

Based on these assumptions, the predicted medicines budget impact was as follows:

Year	Gross	Net
1	£0.7m	£0.7m
2	£5.0m	£4.9m
3	£11.2m	£11.0m
4	£16.8m	£16.4m
5	£21.0m	£20.5m

Note that the market share for the first year was very low and a much more rapid uptake of the medicine seems feasible, suggesting the budget impact above would be accelerated and possibly exceeded.

A value was placed on the resources freed up assuming average cost applied. This is conventional in an economic appraisal, while accepting they may not readily convert into cash-releasing savings. The values estimated were £319k in year 1, rising to £10.4m in year 5. Reduced INR monitoring represented around 60% of these figures, with the remainder comprising costs of treatment of acute events and longer-term disability.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission. The reference shaded in grey is 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 28 July 2011.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public*

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.