

# Review of Supplier Economic Analysis

## Dabigatran Exelilate for the Prevention of Stroke, Systemic Embolism and Reduction of Vascular Mortality in Patients with Atrial Fibrillation

<b>To:</b>	Cardiovascular Subcommittee, PTAC
<b>From:</b>	██████████
<b>Date:</b>	September 2010
<b>Subject:</b>	Review of Cost-Utility Analysis of Dabigatran Exelilate for the prevention of Stroke, Systemic Embolism and Reduction of Vascular Mortality in Patient with Atrial Fibrillation provided by Boehringer Ingelheim NZ Ltd. ██████████

### 1. Summary of Proposal

<b>Pharmaceutical</b> Dabigatran Exelilate (Pradaxa®).
<b>Supplier</b> Boehringer Ingelheim NZ Ltd.
<b>Proposed Indication</b> Prevention of Stroke, Systemic Embolism and Reduction of Vascular Mortality in Patient with Atrial Fibrillation.
<b>Dosing</b> 110mg or 150mg twice daily.
<b>Pharmaceutical Price</b> ██████████ per pack of 60 (110mg and 150mg capsules).
<b>Current Treatment</b> No anticoagulation treatment, aspirin, warfarin or clopidogrel.

## 2. Context

### 2.1 Proposal under Assessment

An application for the funding of dabigatran for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation (AF) was received from Boehringer Ingelheim NZ Ltd in May 2010. The application is to be reviewed by the Cardiovascular Subcommittee in October 2010 and by the Pharmacology and Therapeutic Advisory Committee (PTAC) in November 2010.

### 2.2 Disease and Patient Population

AF is a tachyarrhythmia characterised by predominantly uncoordinated atrial activation with consequent deterioration of mechanical function. AF may occur as a result of numerous cardiovascular (for e.g. ischaemic heart disease or hypertension) and non-cardiovascular conditions (for e.g. thyrotoxicosis). Different types of AF have been defined according to the timing and duration of arrhythmia i.e. paroxysmal, persistent or permanent. Chronic (permanent or persistent) AF is more likely to be observed in older patients and those with additional cardiovascular problems.

Patient management, regardless of the pattern of AF, includes strategies of rate or rhythm control to address the underlying arrhythmia. Stroke prevention with antithrombotic therapy also forms a key part of management of patients with AF. AF is associated with a hypercoagulable state and a predisposition to thrombus formation. The presence of AF is associated with an almost 5-fold excess of stroke compared with its absence.

AF is the most common cardiac arrhythmia in clinical practice and as a consequence of the ageing population, AF is becoming an increasingly important public health burden.

### 2.3 Current Treatment in New Zealand

Current treatment in New Zealand for patients for AF is aspirin, warfarin, no anticoagulation treatment (and clopidogrel).

### 2.4 Pharmaceutical under Assessment

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

In-vivo and ex-vivo animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of thrombosis.

The recommended daily dosage is 300 mg, given orally as 150 mg twice daily. Therapy should be continued life-long. For patients with a potentially higher risk of major bleeding, e.g. age  $\geq 75$  years, a CHADS<sub>2</sub> score of  $\geq 3$ , moderate renal impairment (CrCL 30-50 mL/min), concomitant treatment with strong P-gp inhibitors (e.g. amiodarone, quinidine or verapamil), or previous gastrointestinal bleeding, a reduced daily dose of 220 mg, given as 110 mg twice daily, may be considered.

### 3. Clinical Efficacy

#### *Dabigatran vs. warfarin*

The pivotal RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study published in 2009<sup>1</sup> was a large, multicentre, prospective, randomised trial that compared the efficacy and safety of two fixed dosages of dabigatran etexilate (110 mg twice daily and 150 mg twice daily) with open-label adjusted-dose warfarin therapy over a period of 2 years in a total of 18,113 AF patients at risk of stroke. Patients enrolled in the study had a mean age of 71.5 years and a diagnosis of persistent, paroxysmal or permanent AF with at least one of the following characteristics:

- previous stroke or transient ischaemic attack (IA);
- left ventricular ejection fraction (LVEF)  $< 40\%$ ;
- New York Heart Association (NYHA) class II or higher heart failure symptoms within 6 months of screening and;
- age at least 75 years or age 65 to 74 years plus diabetes mellitus, hypertension or coronary artery disease.

The primary efficacy outcome was stroke or systemic embolism, while the primary safety outcome was major bleeding. Secondary outcomes included stroke (ischaemic/unspecified, haemorrhagic, non-disabling or disabling/fatal), myocardial infarction, pulmonary embolism, TIA, hospitalisation, and death. The net clinical benefit of the treatments was defined as a composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding. The primary analysis was designed to test whether either dose of dabigatran etexilate was non-inferior to warfarin, as evaluated with Cox-proportional-hazards modelling; after non-inferiority of the dabigatran etexilate had been established, all subsequent p-values were determined by two-tailed tests of superiority.

The results of the primary outcome (stroke or systemic embolism) of RELY study showed that both dosages of dabigatran etexilate were non-inferior to warfarin ( $p < 0.001$ ). Rates of the primary outcome were 1.69% per year in the warfarin group, as compared to 1.53% per year in the group that received 110mg of dabigatran (relative risk with dabigatran, 0.91; 95% CI, .74-1.11;  $P < 0.001$  for non inferiority). The 150 mg bd dosage was statistically significant to warfarin in reducing the rate of stroke or systemic embolism (relative risk 0.66; 95% CI 0.53 – 0.82;  $p < 0.001$ ). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110mg bd of dabigatran ( $p=0.13$ ) and 3.64 per year with 150mg bd of dabigatran ( $p=0.051$ ).

The rate of haemorrhagic stroke with warfarin was 0.38% per year, while with dabigatran etexilate 110 mg bd it was 0.12% per year (relative risk 0.31; 95% CI 0.17 - 0.56;  $p < 0.001$ ), and with dabigatran etexilate 150 mg bd it was 0.10% per year (relative risk 0.26; 95% CI 0.14 - 0.49;  $p < 0.001$ ). The 150 mg bd dosage of dabigatran etexilate was statistically significantly superior to warfarin (relative risk 0.76; 95% CI 0.60 - 0.98;  $p = 0.03$ ) for this endpoint.

Major bleeding events were lower with both dosages of dabigatran etexilate compared with dose-adjusted warfarin. The difference vs. warfarin was statistically significant for the 110 mg bd dosage (2.71% vs. 3.36% per year; relative risk 0.80; 95% CI 0.69 - 0.93;  $p = 0.003$ ). With the 150 mg bd dosage, the rate of major bleeding events was marginally lower than with warfarin (3.11% vs. 3.36% per year; relative risk 0.93; 95% CI 0.81 - 1.07;  $p = 0.31$ ). However, the rate of gastrointestinal bleeding (which was a subcategory of major bleeding) was significantly higher with dabigatran at the 150-mg dose than with warfarin (1.51% vs. 1.02% per year; relative risk 1.50; 95% CI 1.10-1.89;  $p < 0.001$ ).

Intracranial haemorrhage was significantly lower with both dosages of dabigatran etexilate than with warfarin (110 mg bd dosage: 0.23% vs. 0.74% per year; relative risk 0.31; 95% CI 0.20 - 0.47;  $p < 0.001$ ; 150 mg bd dosage: 0.30% vs. 0.74% per year; relative risk 0.40; 95% CI 0.27 - 0.60;  $p < 0.001$ ).

From the RELY study, there was no evidence of hepatotoxicity from the serial measurements of liver function undertaken in patients receiving dabigatran etexilate. Dyspepsia was significantly more common with dabigatran etexilate, which occurred in 11.8% and 11.3% of patients in the 110 mg bd and 150 mg bd dosage groups, respectively, as compared with 5.8% of patients in the adjusted-dose warfarin group ( $p < 0.001$  for the comparison of either dose of dabigatran etexilate with warfarin).

### *Dabigatran vs. aspirin*

There are no current direct head to head trials comparing dabigatran vs. aspirin in the prevention of stroke and systemic embolism in people with AF. Therefore, indirect comparisons are made in the supplier CUA using a comparison of warfarin vs. aspirin.

A meta-analysis was conducted by Hart et al (2007)<sup>2</sup> to evaluate the efficacy and safety of antithrombotic agents for stroke prevention in patients who have AF. The meta-analysis included all randomised trials with a mean follow-up period of 3 months or longer that tested antithrombotic agents in patients who have nonvalvular AF (using Cochrane search strategy, 1966-March 2007). Twenty-nine trials were included 28,044 participants (mean age, 71 years, mean follow-up, 1.5 years).

Compared with the control, adjusted-dose warfarin (6 trials, 2900 participants) and antiplatelet agents (8 trials, 4876 participants) reduced stroke by 64% (95% CI, 49-74%) and 22% (95% CI, 6-35%), respectively. Adjusted-dose of warfarin was substantially more efficacious than antiplatelet therapy (relative risk reduction, 39% [CI, 22% to 52%]). This comparison included 12 trials with 12,963 participants. Other randomised comparisons were reported to be inconclusive. Absolute increases in intracranial

haemorrhage were reported to be small (<0.3% per year) on the basis of the meta-analysis.

The authors concluded that adjusted dose of warfarin and antiplatelet agents reduced stroke by approximately 60% and 20%, respectively, in patients who have AF. Warfarin therapy was reported to be substantially more effective (by approximately 40%) than antiplatelet therapy.

Mant et al (2007)<sup>3</sup> evaluated whether warfarin reduced the risk of major stroke, arterial embolism, or other intracranial haemorrhage compared with aspirin in elderly patients. 973 patients aged 75 years or over (mean age 81.5 years) with AF were recruited from primary care and randomly assigned to warfarin (target INR ratio 2-3) or aspirin (75mg per day). The follow up period was for a mean of 2.7 years. The primary endpoint was fatal or disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhagic, or clinically significant arterial embolism.

The Mant study reported the following results:

- that there were 24 primary events (21 strokes, two other intracranial haemorrhagic, and one systemic embolism) in patients assigned warfarin and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in people assigned to aspirin;
- Yearly risk 1.8% vs. 3.8%, relative risk 0.48, 95% CI 0.28-0.80, P=0.003; absolute year risk reduction 2%, 95% CI, 0.7-3.2; and
- Yearly risk of extracranial haemorrhage was 1.4% warfarin vs. 1.6% aspirin, relative risk 0.87, 0.43-1.73; absolute risk reduction 0.2% -0.7 to 1.2.

The authors concluded that the data supported the use of anticoagulation treatment for patients aged over 75 years who have AF, unless they are contraindicated or the patients decides that the benefits are not worth the inconvenience.

#### 4. International Economic Analysis and Recommendations

No international economic evaluations were located from the Scottish Medicines Consortium (SMC), National Institute for Health and Clinical Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), or the Pharmaceutical Benefits Advisory Committee (PBAC) of Australia for the use of dabigatran in the prevention of stroke and systemic embolism in people with atrial fibrillation.

NICE is currently appraising the clinical and cost-effectiveness of dabigatran etexilate within its licensed indication for the prevention of stroke and systemic embolism in people with atrial fibrillation. NICE anticipates these results will be published around June 2011.

The Canadian Agency for Drugs and Technologies in Health (CADTH) has published a health technology report assessing the new anticoagulants dabigatran and rivaroxaban for the prevention of stroke in patients with atrial fibrillation. Although neither drug is approved for this indication in Canada; the health technology assessment (HTA) concludes: patients with excellent INR control on warfarin may not benefit from a change

in therapy, but vitamin K antagonist alternatives could have a role when warfarin is not an option or when the international normalised ratio (INR) cannot be stabilised.

PHARMAC staff are not aware that dabigatran is being registered for the treatment of AF anywhere internationally. Therefore, there is limited availability of international economic analysis and recommendations.

## 5. Economic Analysis

A cost-utility analysis (CUA) was received from Boehringer Ingelheim NZ Ltd. PHARMAC staff have undertaken a rapid review of the supplier CUA. This assessment first reviews and critiques the supplier CUA, and then makes several amendments to the analysis. Please note that this is an initial cost-effectiveness review and further evaluation will be undertaken following advice from the Cardiovascular Subcommittee and PTAC.

The economic evaluation estimated the cost-effectiveness of various proportions of dabigatran, warfarin, aspirin and no treatment for patients 60-89 years old with AF and high or very high risk of ischaemic stroke. A population based Markov model was built which follows 6 age groups and 3 risk thresholds (CHADS<sub>2</sub> ≥ 1, 2, 3) in accordance with the findings from the NZ GP database.

The following table summarises the main inputs and assumptions used in the supplier model:


Model Input / Assumption	Details	PHARMAC Comment
Type of analysis	Cost-Utility Analysis (CUA).	The type of analysis undertaken was appropriate. However, if the recommendation is that dabigatran vs. warfarin has the same or similar effect, the appropriate type of analysis would be cost-minimisation. In this analysis, the yearly cost of dabigatran and the yearly cost of warfarin monitoring, would become the most significant drivers of the result.
Target population	[REDACTED]	The analysis was based on the correct target population (i.e. the target population most likely to receive treatment). The analysis excluded [REDACTED]. The patients excluded are described at being 20% of the total population.  Using [REDACTED] makes the analysis complex.  Further evaluation is required to determine how the assumptions around the target population impact the cost per QALY results.
		The time horizon was appropriate.

<p><b>Time horizon &amp; cycle length</b></p>	<p>[REDACTED]</p>	<p>The cycle length [REDACTED] appears appropriate and justified in terms of the underlying disease and effect of the interventions (dabigatran, warfarin, no anticoagulation treatment and aspirin).</p>
<p><b>Comparator</b></p>	<p>[REDACTED]</p>	<p>The Prescriptions for Pharmacoeconomic Analysis (PFPA) states 'In cases where treatment regimens differ substantially throughout NZ, it is recommended that a range of comparators be used in the analysis. The results of the different analysis should be reported separately, as well as reporting a weighted-average (weighted by patient numbers prescribed comparator treatment) of the cost per QALY result'</p> <p>Therefore, it would have been appropriate to model the following comparators and reported each result separately:</p> <ul style="list-style-type: none"> <li>• Dabigatran vs. warfarin;</li> <li>• Dabigatran vs. aspirin;</li> <li>• Dabigatran vs. no treatment.</li> </ul> <p>Then report the weighted-average of the cost per QALY result (weighted by patient numbers prescribed the comparator treatment [REDACTED])</p> <p>[REDACTED] The approach would have been more transparent when the cost per QALY results was reported, instead of appearing complex.</p> <p>PHARMAC staff would like advice from the Subcommittee and PTAC on the relevance of the use of no anticoagulant treatment as a comparator in the supplier analysis?</p> <p>It was appropriate to exclude clopidogrel from the analysis as this treatment is currently not widely used for the treatment of AF in NZ. However, since this evaluation was completed clopidogrel was open listed for all indications (September 2010 due to a significant price reduction). Therefore, if the use of clopidogrel for AF is likely to increase it would become an appropriate comparator for this analysis.</p>
<p><b>Treatment regimen (including dose)</b></p>	<p>[REDACTED]</p>	<p>Dose adjustments are likely with the use of warfarin over time, however, this does not impact the total cost of warfarin substantially as the current Pharmaceutical Schedule costs between all warfarin tablet strengths are similar.</p>

<p><b>Efficacy</b></p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>Further assessment regarding the quality of the evidence is subject to review by the Cardiovascular Subcommittee and PTAC.</p> <p>The model appears to be based on the best quality data available. The sources of data used in the model appear to be clearly stated.</p> <p>Further evaluation (and clinical trials) may be required to determine the efficacy of dabigatran vs. aspirin; and evaluation as to whether the use of the Hart meta-analysis was the most appropriate data source to determine the efficacy of warfarin vs. aspirin.</p>
<p><b>Health states and model structure</b></p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>Justification to the choice of health states within the model is provided and important health states do not appear to have been excluded from the model.</p> <p>The complexity of the model combined with a lack of sensitivity analysis made the initial evaluation by PHARMAC staff challenging. Further evaluation is required to determine the true extent of modelling uncertainty.</p> <p>Further evaluation is required to determine the assumptions around the use of the NZ General Practice data to inform the epidemiology and population based Markov model.</p>
<p><b>Sensitivity analysis</b></p>	<p>[REDACTED]</p>	<p>The supplier has not conducted sufficient sensitivity analysis to fully determine the cost-effectiveness of dabigatran.</p> <p>This area of the reporting of the results</p>





		<p>per hour. Therefore, if 3 hours of additional nurse time per year is correct, this cost has been slightly underestimated due to a lower hourly cost of [REDACTED] used in the supplier analysis.</p> <p>Further sensitivity analysis is required to test the impact of warfarin monitoring on the overall results.</p> <p>The cost of the relevant outcomes appears to have been slightly overestimated. Some of these costs have been estimated from Australian costs and adjusted to NZ costs.</p> <p>The following non pharmaceutical costs for the relevant outcomes at 1 year should be amended as following (further evaluation is required to determine the annual costs after recovery and the first year)</p> <ul style="list-style-type: none"> <li>• Stroke = \$6,406 (based on an average of DRG costs B70A, B70B, B70C). Further evaluation is required to validate the estimated cost of a stroke, due to the large difference between the cost the supplier has used and the DRG costs. Regardless of the actual cost of a stroke, it is likely that the supplier has overestimated this cost;</li> <li>• Acute MI =\$5,692 (based on TAR 99);</li> <li>• Systemic Embolism =\$5,102 (based on an average of DRG costs E61A, E61B);</li> <li>• TIA = \$2,605 (based on an average of DRG costs B69A, B69B).</li> </ul> <p>It does not appear that any important costs have been excluded from the analysis, however, as the supplier has not conducted appropriate sensitivity analysis on these cost inputs, further evaluation is required to fully determine the impact of these cost estimates on the overall cost per QALY results.</p>
<b>Discount rate</b>	The costs and benefits were discounted at 3.5%.	The correct discount rate was used.

In the supplier analysis the cost per QALY result varied according to the substitution options (from 1-32) as given in the potential new practice. The cost per QALY result varies from [REDACTED]. The sensitivity analysis conducted by the supplier gives a range of cost per QALY result from [REDACTED]. The sensitivity analysis

conducted by the supplier is not sufficient to be confident of the relative cost-effectiveness of dabigatran.

PHARMAC staff made several amendments to the analysis and considered that dabigatran should be compared with each comparator treatment separately, as well as reporting a weighted-cost per QALY result. Therefore, the following comparisons were made (based on the current supplier assumptions) and reported separately:

- Dabigatran vs. warfarin;
- Dabigatran vs. aspirin;
- Dabigatran vs. no anticoagulant treatment.

The results for these amendments based on the Markov model provided by the supplier showed the following results:

Pharmaceutical	Incremental Cost	Incremental QALY	Cost per QALY	Interpretation
Dabigatran vs. warfarin	██████████	-0.017	██████████	Dabigatran ██████████ is less effective than warfarin, therefore, is not cost-effective.
Dabigatran vs. aspirin	██████████	0.23	██████████	-
Dabigatran vs. no Treatment	██████████	0.57	██████████	Dabigatran ██████████ is more effective than no treatment.

The results show that when dabigatran was compared with warfarin, ██████████ and was less effective than warfarin. Therefore, the model shows that when an individual comparison is made of dabigatran vs. warfarin, ██████████

The results show that when dabigatran is compared to aspirin, the cost per QALY result is approximately ██████████. However, PHARMAC staff note that it is unlikely that only warfarin intolerant patients would access dabigatran and that the result would be a lot higher if a significant portion of patients would use dabigatran instead of warfarin. In addition it is uncertain whether the efficacy of dabigatran compared to aspirin has been assessed correctly.

PHARMAC staff consider that insufficient evidence has been presented to draw any firm conclusions about the cost-effectiveness of dabigatran compared to either warfarin or aspirin. Further evaluation will be undertaken following advice from the Cardiovascular Subcommittee and PTAC.

**References:**

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran vs. Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2009; 361:1139-51.
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3. Mant J, Hobbs R, Fletcher K, et al. Warfarin vs. Aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007; 370: 493-503.
4. CADTH. Issues in Emerging Health Technologies. New Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation. 2010. Issue 116. March 2010.

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