

PHARMACEUTICAL SCHEDULE APPLICATION

From: [REDACTED]

Date: September 2010

Dabigatran for atrial fibrillation

SUMMARY OF PHARMACEUTICAL			
Brand Name	Pradaxa	Chemical Name	Dabigatran
Indications	Atrial Fibrillation	Presentation	110mg and 150mg capsules
Therapeutic Group	Sub-group (group)	Dosage	110mg to 150mg BID
Supplier	Boehringer Ingelheim	Application Date	May 2010
MOH Restrictions	Prescription medicine	Proposal type	New Listing
Proposed Subsidy	[REDACTED] pack of 60 (110mg and 150mg capsules)	Manufacturer's Surcharge	Nil
Proposed Restriction	Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.		
OP	No	Section F	No
Market Data	YE 30 June 2011	YE 30 June 2012	YE 30 June 2013
Number of Patients¹	[REDACTED]	[REDACTED]	[REDACTED]
Subsidy (gross)	[REDACTED]	[REDACTED]	[REDACTED]
Net Cost to Schedule²	[REDACTED]	[REDACTED]	[REDACTED]
Net Cost to DHBs³	[REDACTED]	[REDACTED]	[REDACTED]
Net Cost to DHBs (NPV)	[REDACTED]		

Notes: NPV = Net present value; OP = Original pack


1. These are supplier estimates. See Patient Numbers section in paper below for assumptions.

2. Net Cost to Schedule = Subsidy (gross) – drug cost of warfarin and aspirin (assumes 80% of patients currently on aspirin, 20% on warfarin).

3. Net Cost to DHBs = Net Cost to Schedule – cost of warfarin monitoring (\$540 per patient per year).

QUESTIONS TO PTAC

1. What is the strength and quality of the evidence supplied in the application?
 - 1.1. What is the strength and quality of evidence for dabigatran vs. warfarin?
 - 1.2. What is the strength and quality of evidence for dabigatran vs. aspirin?
2. Does dabigatran have the same or similar therapeutic effect to any pharmaceuticals currently listed on the Pharmaceutical Schedule? If so, which pharmaceutical (or therapeutic sub-group) and at what dose does it have the same or similar effect?
3. With which pharmaceuticals would dabigatran be used in combination, and which pharmaceuticals would it replace?
4. What proportions of patients with AF are currently receiving no treatment, aspirin, warfarin or clopidogrel plus aspirin? What proportions of patients with AF from current treatment, do you consider would switch to the use of dabigatran?
5. What is the strength and quality of evidence to support the use of clopidogrel and aspirin in combination for thromboprophylaxis in AF?
6. Are there currently any problems with access to and / or availability of alternative treatments?
7. Does dabigatran provide any additional health benefit or create any additional risks compared with other treatment options? If so, what benefits or risks are different from alternative treatments?
8. Which patient population(s) would benefit most from dabigatran? How big are these patient populations and what are the absolute risk reductions for the various possible treatments for these patient populations?
 - 8.1. Are aspirin or aspirin and clopidogrel potential alternatives in these patient groups?
9. Is there any unmet health need in this population, or within a subset of this population (e.g. Maori / Pacific people)?
10. Should any restrictions be placed on the use of dabigatran? If so, for what reason should these restrictions be applied?
 - 10.1. Is the CHADS₂ scoring system a commonly used and accepted clinical classification system in New Zealand? If not, what would be a more appropriate classification system?
 - 10.2. Does the Committee consider that it would be possible to restrict dabigatran to patients who have a CHADS₂ score ≥ 2 and are contraindicated to or have failed warfarin therapy?
 - 10.3. Does the Committee have any other suggestions as to how dabigatran could be appropriately targeted given that it is an expensive drug?
11. Does the Committee recommend funding both strengths of dabigatran i.e. 110mg and 150mg?
 - 11.1. What is the strength and quality of evidence supporting the supplier's recommendation for the reduced of 220mg/day be considered in patients with a potentially higher risk of major bleeding, for e.g. age ≥ 75 years, a CHADS₂ score of ≥ 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?

12. Would the use of dabigatran create any significant changes in health-sector expenditure other than for direct treatment costs (e.g. diagnostic testing, nursing costs or treatment of side-effects)?
- Approximately how many warfarin INR monitoring tests do you consider would be done per year for each warfarin patient? Do you consider that INR monitoring creates additional GP visits (If so approximately how many per year?) Do you consider that INR monitoring creates additional practice nurse costs?
13. What effects would the listing of dabigatran in the Pharmaceutical Schedule have on the current market dynamics for the alternative treatments?
14. Should dabigatran be listed in the Pharmaceutical Schedule?
- Name the decision criteria particularly relevant to a positive or negative recommendation and explain why each is relevant.
15. If listing is recommended, what priority rating would you give to this proposal? [low / medium / high / only if cost-neutral]?
16. 
17. Does the Committee have any recommendations additional to the application?

DISCUSSION

Background

Pradaxa (dabigatran etexilate) was previously reviewed by PTAC in November 2008 for the prevention of venous thromboembolism following orthopaedic surgery. The Committee recommended that dabigatran be declined for a listing in Section B of the Pharmaceutical Schedule but that it be listed on the Discretionary Community Supply (DCS) list with a low priority for patients following knee and hip orthopaedic surgery available for durations of up to 10 days and 35 days respectively (see Appendix 1 for minutes).

Boehringer Ingelheim (Boehringer) has submitted an application for the use of dabigatran (75mg) in the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation (AF). It is not yet registered for this indication in New Zealand or any other country, although Boehringer anticipates registration in New Zealand by the end of the year.

The submission from Boehringer is summarised below with the incorporation of some additional information from PHARMAC staff.

Disease Targeted

Atrial fibrillation (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 (e.g. ischaemic heart disease or hypertension) and non-cardiovascular conditions (e.g. thyrotoxicosis). Different types of AF have been defined according to the timing and duration of the arrhythmia for e.g 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 as AF is associated with a hypercoagulable state and a predisposition to thrombus formation. AF is associated with an almost 5-fold increase in stroke incidence.

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

Current Treatments

The risk of stroke for a patient may be estimated based on the presence or absence of clinical risk factors, including AF. Stroke risk classification schemes group patients into high, intermediate and low risk categories. A number of clinical classification algorithms have been proposed for predicting the risk of stroke in patients with AF. The main internationally recognised algorithms are:

- American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC)
- American College of Chest Physicians (ACCP)
- Atrial Fibrillation Investigators (AFI)
- Stroke Prevention in Atrial Fibrillation Investigators (SPAF)
- CHADS₂
- Framingham Heart Study

The Best Practice Guideline developed by the New Zealand Guidelines Group (May 2005), informed by the Framingham Study risk equation, recommends that all patients with AF (whether paroxysmal, persistent or permanent) should have their thromboembolic risk assessed. Warfarin is recommended for patients at intermediate to high risk of stroke, while aspirin is suggested for those at low risk, although treatment should be individualised based on the balance of risks and benefits for each patient.

Warfarin

Vitamin K antagonists (VKAs) are the current gold standard in patients eligible and suitable for long-term anticoagulation. They produce an anticoagulant effect by inhibiting synthesis of four vitamin K-dependent clotting factors: II, VII, IX and X. Warfarin sodium (Coumadin[®] or Marevan[®]) is the most frequently used VKA.

In the most recent meta-analysis to be published (Hart et al. 2007), when compared with placebo or no treatment, adjusted-dose warfarin (six trials, 2900 participants) reduced the risk of stroke by 64%. Adjusted-dose warfarin was also substantially more efficacious than antiplatelet agents (12 trials, 12,963 participants) with a relative risk reduction of 39%.

Use of VKAs is complicated by the need to maintain a balance between optimising the therapeutic effect and minimising the risk of serious adverse events such as bleeding. For stroke prophylaxis in patients with AF, the recommended target INR range is 2.0 to 3.0. Under-anticoagulation increases the risk of ischaemic stroke while over-anticoagulation can result in haemorrhage, including intracerebral haemorrhage (ICH). In a study of 74 patients with AF hospitalised for ischaemic stroke while taking warfarin, the odds of stroke compared

with the risk at an INR of 2.0, doubled at an INR of 1.7, tripled at an INR of 1.5, and increased 6-fold at an INR of 1.3 (Hylek et al. 1996-attached in Appendix 2). Although the incidence of ICH is low (typically between 0.1% and 0.6%), there is an increased risk at INRs ≥ 3.5 (adjusted relative odds of 4.6) when compared to INRs 2.0-3.0 (Fang et al. 2004-attached in Appendix 2).

A number of factors affect the ability to maintain INRs within the target therapeutic range (TTR), including:

- Variable responsiveness to VKAs
- Drug-drug and drug-food interactions
- The complexity of the dosing regimen, which requires patient education

Intensive monitoring is required for the duration of therapy to ensure that the anticoagulant effect is maintained within the recommended target therapeutic range. Evidence suggests that testing more frequently than every 4 weeks may lead to greater time in the therapeutic range. However, even in a well-controlled population monitored at a university teaching hospital, where patients had INR tests 23 times a year on average, AF patients treated with warfarin were outside the INR target range 32.1% of the time (Jones et al. 2005).

Despite the established need for stroke prevention in patients with AF and clearly defined guidelines for the use of effective treatments, the picture in clinical practice is somewhat different. In clinical practice, it is difficult to maintain INRs within the target therapeutic range and the encouraging results seen in large, well-controlled trials are often not replicated in clinical practice.

PHARMAC staff note that, based on NHI number-linked PharmHouse data, there are currently approximately 55,000 patients dispensed warfarin in New Zealand for various indications. The drug cost of warfarin is approximately \$30-\$60 per patient per year. The supplier estimates that the total cost of warfarin monitoring would be approximately \$540 per patient per year. This assumes that patients are tested 2-weekly, at a cost of \$14 per test and also includes costs of clinician time.

Aspirin

The antiplatelet agent aspirin (acetylsalicylic acid; ASA) is recommended for patients at low risk of stroke and for those in the moderate-to-high risk category who refuse or cannot tolerate VKAs or for whom VKAs are contraindicated. In a meta-analysis, aspirin (7 trials, 3990 participants) reduced the risk of stroke in patients with non-valvular AF by 19% (relative risk reduction, 95% CI, -1% to 35%) versus placebo/control (Hart et al. 2007) with an absolute risk reduction of 2.5% per year (NNT = 40) when used in secondary prevention. However, adjusted-dose warfarin was found to be substantially more efficacious than antiplatelet agents with a relative risk reduction of 39% (Hart et al. 2007).

PHARMAC staff identified another study – the BAFTA study (Mant et al 2007 – see attached in Appendix 3) which was a prospective randomised open-label trial with blind assessments of endpoints which assessed whether warfarin reduced the risk of major stroke, arterial embolism, or other intracranial haemorrhage compared with aspirin in 973 elderly patients (≥ 75 years). This study was not included in the meta-analysis (Hart et al. 2007) mentioned above. The BAFTA study showed that treatment with warfarin resulted in an absolute risk reduction of 2% (95% CI 0.7-3.2) in primary events (strokes, intracranial haemorrhage and systemic embolism) compared to aspirin.

Based on NHI data, PHARMAC staff note that there are approximately 300,000 patients on aspirin in New Zealand currently for various indications. The drug cost of aspirin is approximately \$5.00 per patient per year.

Clonidogrel plus aspirin

PHARMAC staff note that there has been two large randomised trials which investigated the safety of dual antiplatelet therapy in patients with AF. ACTIVE W compared clonidogrel plus aspirin to warfarin and ACTIVE A compared clonidogrel plus aspirin to aspirin alone in patients who were not candidates for anticoagulation with a VKA (see clinical papers in Appendix 4).

The ACTIVE W trial included 6706 patients who were randomly assigned to combined therapy with clonidogrel (75 mg/day) and aspirin (75 to 100 mg/day) or to oral anticoagulation with a vitamin K antagonist (target INR 2.0 to 3.0). The trial was stopped at an interim analysis after a median follow-up of 1.3 years because warfarin anticoagulation was associated with a significantly lower annual rate of the primary end point (3.9 versus 5.6 percent, relative risk 0.69, 95% CI 0.57-0.85). Although the overall rate of bleeding was significantly increased in the dual antiplatelet group (15.4 versus 13.2 percent per year), there was no significant difference in major bleeding (2.4 versus 2.2 percent per year).

The ACTIVE A trial included 7554 patients with AF who were not candidates for anticoagulation and were randomly assigned to combined therapy with clonidogrel (75 mg/day) and aspirin (75 to 100 mg/day) or to aspirin alone at the same dose. The reasons that patients were not considered candidates for anticoagulation included the physician's judgment that such treatment was inappropriate (50%), a specific risk for bleeding (23%), and strong patient preference (26%). The primary end point, as in ACTIVE W, was the first occurrence of stroke, systemic (non-central nervous system) embolisation, MI, or vascular death.

After a median follow-up period of 3.6 years, patients treated with clonidogrel plus aspirin had a significantly lower annual rate of the primary combined end point (6.8% versus 7.6%, RR 0.89, 95% CI 0.81-0.98; $p=0.01$), which was primarily driven by a reduction in stroke (2.4% versus 3.3%, RR 0.72, 95% CI 0.62-0.83; $p<0.001$). On the other hand, dual antiplatelet therapy was associated with a significant increase in the incidence of major bleeding (2.0% versus 1.3% per year, RR 1.57, 95% CI 1.29-1.92; $p<0.001$).

Dabigatran

Dabigatran etexilate is a small molecule prodrug that is converted to the active principle, dabigatran, by esterase-catalysed hydrolysis in the plasma and liver. Dabigatran is a competitive, reversible, direct thrombin inhibitor. Since thrombin is a plasma serine protease that catalyses the conversion of fibrinogen into fibrin during the coagulation cascade its inhibition by dabigatran prevents the development of thrombi.

The maximum plasma concentration (C_{max}) of dabigatran is attained within 2 hours after administration, indicating rapid absorption and conversion to the active drug. After reaching the C_{max} , plasma concentrations of dabigatran show a biexponential decline characterised by a rapid distribution phase, during which concentrations fall to <30% of the peak level within 4 to 6 hours of administration, followed by a prolonged elimination phase with a mean terminal half-life of 12 to 17 hours (Stangier 2008). Plasma concentration-time profiles in older subjects are similar to those in younger individuals, although plasma concentrations after equivalent doses of dabigatran etexilate are 1.7 to 2-fold higher in older subjects in

comparison with healthy young volunteers, which is likely due to reduced renal function in the elderly and the fact that dabigatran, is mainly eliminated by renal excretion.

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 6.5%. Following multiple oral doses, stable trough plasma concentrations of dabigatran, indicating achievement of steady state, are attained after 2 to 3 days. Elimination of dabigatran is mainly via renal excretion, primarily as the unchanged drug, although small amounts are excreted in the urine as dabigatran glucuronides; faecal excretion accounts for around 6% of an administered dose.

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 ≥ 75 years, a CHADS₂ score of ≥ 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.

Clinical data

The available clinical evidence supporting the inclusion of dabigatran etexilate (for prevention of stroke or systemic embolism and reduction of vascular mortality in patients with atrial fibrillation) is derived from two studies. Firstly there is the short-term PETRO (Prevention of Embolic and Thrombotic Events in Patients with Persistent AF) study, which was a pilot study designed to identify a safe dosage of dabigatran etexilate in patients with AF (Ezekowitz et al. 2007-see attached in Appendix 5). Secondly there is the much larger, long-term RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study, which was designed to compare the efficacy of two fixed doses of dabigatran etexilate with dose-adjusted warfarin in patients with AF over a period of 2 years (Connolly et al. 2009).

Study 1 - The primary outcome of the PETRO short-term dose escalation pilot study (Ezekowitz et al. 2007), which was conducted in 502 patients with AF at high risk of thromboembolic events, was the frequency of bleeding events at the dosages used (i.e. 50 mg, 150 mg and 300 mg dabigatran etexilate twice daily combined with either no aspirin or 81 mg or 325 mg aspirin once daily). This study established a dose-response for bleeding and an upper limit of tolerability of 300 mg dabigatran etexilate twice daily (plus aspirin), based on the frequency of major and clinically significant bleeding events. As the duration of the trial was only 12 weeks and the frequency of thromboembolic events in the study population was low, no efficacy conclusions were able to be reached.

Study -2 The pivotal RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study 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 (Connolly et al. 2009). 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 TIA; 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 RE-LY study showed that for:

- *Stroke or systemic embolism (primary outcome of the study)*
Both dosages of dabigatran etexilate were non-inferior to warfarin ($p < 0.001$). Additionally, the 150 mg bid dosage was statistically significantly superior to warfarin in reducing the rate of stroke or systemic embolism (relative risk 0.66; 95% CI 0.53 – 0.82; $p < 0.001$) with an absolute risk reduction (ARR) of 0.58% and number needed to treat (NNT) of 172.
- *Major bleeding events (primary safety outcome)*
They were lower with both dosages of dabigatran etexilate than with dose-adjusted warfarin. The difference versus warfarin was statistically significant for the 110 mg bid dosage (2.71% vs. 3.36% per year; relative risk 0.80; 95% CI 0.69 – 0.93; $p = 0.003$; ARR of 0.65%; NNT = 154). With the 150 mg bid 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; $p = 0.31$; ARR of 0.25%; NNT = 400). 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; $p < 0.001$; ARR of 0.49%; NNT = 204).
- *Intracranial haemorrhage*
This was significantly lower with both dosages of dabigatran etexilate than with warfarin (110 mg bid dosage: 0.23% vs. 0.74% per year; relative risk 0.31; 95% CI 0.20 – 0.47; $p < 0.001$; ARR of 0.51%; NNT = 196; -150 mg bid dosage: 0.30% vs. 0.74% per year; relative risk 0.40; 95% CI 0.27 – 0.60; $p < 0.001$; ARR of 0.44%; NNT = 227).
- *Haemorrhagic stroke*
Although low, there were about one-third of those with adjusted-dose warfarin with both dosages of dabigatran etexilate. The rate of haemorrhagic stroke with warfarin was 0.38% per year, while with dabigatran etexilate 110 mg bid it was 0.12% per year (relative risk 0.31; 95% CI 0.17 – 0.56; $p < 0.001$; ARR of 0.26%; NNT = 385), and with dabigatran etexilate 150 mg bid it was 0.10% per year (relative risk 0.26; 95% CI 0.14 – 0.49; $p < 0.001$; ARR of 0.28%; NNT = 357). This is an important finding as intracranial haemorrhage is considered the most devastating complication of warfarin.
- *Ischaemic or unspecified stroke*
The 150 mg bid dosage of dabigatran etexilate was statistically significantly superior to warfarin (relative risk 0.76; 95% CI 0.60 – 0.98; $p = 0.03$; ARR of 0.28%; NNT = 357) for this endpoint.
- *Rates of hospitalisation and of death from vascular or any cause*
They were lower with the two dabigatran etexilate dosages than with adjusted-dose warfarin, and the differences versus warfarin reached statistical significance with the 110 mg bid dosage for hospitalisations (19.4% vs. 20.8% per year; relative risk 0.92; 95% CI 0.87 – 0.97; $p = 0.0003$; ARR of 1.4%; NNT = 71) and with the 150 mg bid dosage for deaths from vascular causes (2.28% vs. 2.69% per year; relative risk 0.85; 95% CI 0.72 – 0.99; $p = 0.04$; ARR of 0.41%; NNT = 224).
- *Rates of myocardial infarction*

These were higher with both dosages of dabigatran etexilate in comparison with dose-adjusted warfarin (0.72% per year in the 110 mg group (relative risk, 1.35; 95% CI, 0.98 to 1.87; P = 0.07) and 0.74% per year in the 150 mg group (relative risk, 1.38, 95% CI, 1.00 to 1.91; P = 0.048) with the two dosages of dabigatran etexilate versus 0.53% per year with adjusted-dose warfarin). The explanation for this finding is uncertain, but may be related to better protection against coronary ischaemic events by warfarin.

- *The net clinical benefit outcome (a composite measure of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death or major bleeding)*
This was better with both dosages of dabigatran etexilate in comparison with dose-adjusted warfarin, though the difference versus warfarin was statistically significant only for the 150 mg bid dosage of dabigatran etexilate. The rates of this combined outcome measure were 7.64% per year with warfarin as compared with 7.09% per year with dabigatran etexilate 110 mg bid (relative risk 0.92; 95% CI 0.84 – 1.02; p = 0.10; ARR of 0.55%; NNT = 182), and 6.91% per year with dabigatran etexilate 150 mg bid (relative risk 0.91; 95% CI 0.82 – 1.00; p = 0.04; ARR of 0.73%; NNT = 137).

In the RE-LY trial, the mean percentage of the study period during which the INR was within the therapeutic range for patients treated with warfarin was 64%, which according to the supplier was similar to findings in other trials.

PHARMAC staff note that there are no trials directly comparing dabigatran and aspirin. This is relevant as aspirin could be considered a comparator to dabigatran if it is restricted to second-line treatment after warfarin. The absolute risk reduction with warfarin treatment versus aspirin range from 0.2-7% based on trials included in the Hart et al 2007 meta-analysis and the BAFTA study (Mant et al. 2007 - see attached in Appendix 3). Results from the RE-LY trial indicate that dabigatran (150mg BID dose) significantly reduced the incidence of stroke and systemic embolism with an absolute risk reduction of 0.58% when compared to warfarin.

Unlike an earlier direct thrombin inhibitor, ximelagatran, which was found to be hepatotoxic and has now been withdrawn, there was no evidence of hepatotoxicity from the serial measurements of liver function undertaken in patients receiving dabigatran etexilate in the RE-LY study. The only adverse effect that was significantly more common with dabigatran etexilate was dyspepsia, which occurred in 11.8% and 11.3% of patients in the 110 mg bid and 150 mg bid 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 with warfarin).

The increased incidence of dyspeptic symptoms with both dosages of dabigatran and the increased risk of gastrointestinal bleeding with the 150 mg bid dosage in comparison with warfarin (see above) may be related, in part, to the acidity of the capsule formulation. As a low pH is required to enhance absorption of the drug from the gastrointestinal tract, the capsules contain dabigatran etexilate-coated pellets with a tartaric acid core.

Other Future Products

PHARMAC staff note that there are other oral anticoagulants in various stages of development including apixaban, rivaroxaban, edoxaban and betrixaban.

Patient numbers



- patients unsuitable for warfarin are currently using aspirin and would be switched to

[REDACTED]

[REDACTED]

Estimated Incremental Cost of Listing with Dabigatran

The yearly costs of treatment with warfarin and aspirin are approximately \$30 and \$5, respectively. Dabigatran drug cost per year is approximately [REDACTED]. Based on the supplier's estimates of patient numbers with various assumptions as detailed in the section above, the total drug cost for dabigatran would be [REDACTED] in year one rising to [REDACTED] by year three.

In calculating the net drug cost to the Pharmaceutical Schedule, PHARMAC staff have assumed that out of the patients who would be treated with dabigatran, 80% would have otherwise been on aspirin and 20% on warfarin. This is based on the supplier's assumption that dabigatran would be restricted to second-line therapy after warfarin. Due to the low costs of the current available alternatives; warfarin and aspirin, this proposal is estimated to be a cost of [REDACTED] (5 years NPV, 8% discount rate) to DHBs even after taking into account the costs of warfarin monitoring.

However, PHARMAC staff note that cost-offsets like reduced hospitalisations through the reduction in ischaemic events have not been taken into account at this stage. We also note that although the supplier has recommended that dabigatran could be restricted to certain patient groups as second-line therapy after warfarin, the restriction would be difficult to enforce, possibly resulting in a high slippage rate (i.e. its use extending to other patient groups, beyond the restrictions, who gain less benefit).

International Prices

Country	Source	Strength	Pack Size	Local Price	Exchange Rate	Price (\$NZ)
Proposal		110mg	60	[REDACTED]		[REDACTED]
		150mg	60	[REDACTED]		[REDACTED]
United Kingdom*	BNF	110mg	60	£112.00	0.4451	\$251.63
Australia*	PBS	110mg	60	\$190.72	0.7971	\$239.29

Note: The 150mg strength capsule is not registered or funded in New Zealand or other countries at the time of writing hence comparisons cannot be provided.

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. This is likely to be due to dabigatran not yet being registered internationally.

The FDA has published briefing information^{1,2} for dabigatran which was reviewed by the Cardiovascular and Renal Drugs Advisory Committee in September 2010. The committee's support for the submission came primarily from the RELY trial. The overall recommendation on regulatory action was that dabigatran should be approved for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The 150 mg dose of dabigatran should be approved but ¹not the 110 mg dose and a superiority claim over warfarin should not be granted. A decision is expected from the FDA following the committee's recommendation by 19 October 2010.

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 (Attached in Appendix 6 – note this does not detail cost-effectiveness). Although neither drug is approved for this indication in Canada; the health technology assessment 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 INR cannot be stabilised.

Cost-effectiveness

A cost-utility analysis (CUA) was received from Boehringer Ingelheim NZ Ltd. PHARMAC staff have undertaken a rapid review of the supplier CUA (Attached in Appendix 7). 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 estimates the cost-effectiveness of [REDACTED] with AF and high or very high risk of ischaemic stroke using dabigatran, warfarin, aspirin and having no treatment. The supplier assumed [REDACTED]. The cost per QALY result varied from [REDACTED] according to the different options (from 1-32). The sensitivity analysis conducted by the supplier provided a range of cost per QALY result from [REDACTED].

1

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM226011.pdf>

2

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM226012.pdf>

In addition to determining a cost per QALY based on a weighted average for all the treatments, it is useful to compare dabigatran to each comparator treatment separately. Using the supplier assumptions and its Markov model this results in the following:

Pharmaceutical	Incremental Cost	Incremental QALY	Cost per QALY	Interpretation
Dabigatran vs. Warfarin	██████	██████	██████	Dabigatran ██████ is less effective than warfarin, therefore, is not cost-effective
Dabigatran vs. Aspirin	██████	██████	██████	-
Dabigatran vs. No Treatment	██████	██████	██████	Dabigatran ██████ is more effective than no treatment

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

The results also indicate that when dabigatran is compared with 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 cost per QALY result would be a lot higher (i.e. less cost-effective) if a significant portion of patients were to use dabigatran instead of warfarin. In addition, it is uncertain whether the efficacy of dabigatran compared with 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 with either warfarin or aspirin. Further evaluation will be undertaken following advice from the Cardiovascular Subcommittee and PTAC.

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Appendices

Appendix 1: PTAC minutes (November 2008) on dabigatran for VTE prophylaxis post orthopaedic surgery.

Appendix 2: Hylek et al 1996 and Fang et al 2004

Appendix 3: BAFTA study (Mant et al 2007)

Appendix 4: Active-A and Active-W clinical papers.

Appendix 5: PETRO study (Ezekowitz 2007)

Appendix 6: CADTH assessment of dabigatran for AF.

Appendix 7: Review of Supplier Economic Analysis. Dabigatran Etexilate for the Prevention of Stroke, Systemic Embolism and Reduction of Vascular Mortality in Patients with Atrial Fibrillation. September 2010.

Supplier's submission provided separately.

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Decision Criteria

1. The health needs of all eligible people within New Zealand;
2. The particular health needs of Maori and Pacific peoples;
3. The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;
4. The clinical benefits and risks of pharmaceuticals;
5. The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;
6. The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule;
7. The direct cost to health service users;
8. The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere; and
9. Such other criteria as PHARMAC thinks fit.

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CHECKLIST FOR PTAC PAPERS

Paper: Dabigatran for Atrial Fibrillation
Date of Meeting: November 2010

All relevant information from the following sources has been included in the paper or is attached:

- / Supplier
- Clinicians
- PHARMAC-initiated literature searches
- PTAC requests for information
- Other _____

Principal Author: [REDACTED]

Other Authors: [REDACTED]

Reviewer(s): [REDACTED]
[REDACTED]

Approved:

For Medical Director

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