

MEMORANDUM FOR BOARD MEETING OF 27 MAY

To: PHARMAC Directors

From: [REDACTED]

Date: May 2011

Listing of dabigatran for atrial fibrillation and VTE prophylaxis following orthopaedic surgery

Recommendations

It is recommended that having regard to the decision criteria set out in Section 2.2 of PHARMAC's Operating Policies and Procedures you:

resolve to list Pradaxa (dabigatran) in the Oral Anticoagulants therapeutic subgroup, Blood and Blood Forming Organs therapeutic group of Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 July 2011 at the following prices/subsidies (ex-manufacturer, excl. GST);

Pharmaceutical	Brand	Form	Strength	Pack Size	Packaging	Proposed subsidy/price
Dabigatran	Pradaxa	Capsules	75mg	60 OP	Bottle	\$148.00
Dabigatran	Pradaxa	Capsules	110mg	60 OP	Bottle	\$148.00
Dabigatran	Pradaxa	Capsules	150mg	60 OP	Bottle	\$148.00

resolve to include a tablet restriction on the 75 mg dose – no more than 2 tabs per day;

resolve to apply Original Pack dispensing to dabigatran in the bottle packaging;

resolve to include a restriction in Section B of the Pharmaceutical Schedule that dabigatran will not be funded Close Control in amounts less than 4 weeks of treatment;

resolve to approve the 1 April 2011 agreement with Boehringer Ingelheim (NZ) Limited subject to the Chief Executive not delaying implementation (as below);

resolve to direct the Chief Executive to delay implementation if the PHARMAC initiated working group has not produced guidance for DHB hospitals on how to manage dabigatran-associated bleeding by 12 June 2011;

note that the agreement with Boehringer Ingelheim (NZ) Limited allows an alternative blister pack packaging to be listed and PHARMAC intends to list it once it becomes available instead of the bottle packaging to avoid the need for ongoing Original Pack dispensing; and,

resolve that the consultation on this proposal was appropriate, and no further consultation is required.

SUMMARY OF PHARMACEUTICAL				
Brand name	Pradaxa	Chemical name	Dabigatran	
Therapeutic Group	Blood and Blood Forming Organs	Presentation	Capsules	
Supplier	Boehringer Ingelheim	Proposal type	New listing	
MoH Restriction	Prescription medicine	Application date	01-Dec-2009	
Section F	No	Original pack	Yes	
Proposed restriction	None			
Brand - Formulation - Packsize	Current subsidy	Proposed subsidy	Price	Manufacturer's surcharge
Pradaxa - Capsules 75mg - 60		\$148.00	\$148.00	Nil
Pradaxa - Capsules 110mg - 60		\$148.00	\$148.00	Nil
Pradaxa - Capsules 150mg - 60		\$148.00	\$148.00	Nil
Market data	Year ending	30 Jun 2012	30 Jun 2013	30 Jun 2014
Number of patients				
Number of Maori or PI people				
Community Pharmaceuticals	Subsidy (gross)			
	Net cost to Schedule			
	Net distribution costs			
	Net cost to DHBs			
	Net present value			
Hospital Pharmaceuticals	Expenditure (gross)			
	Net cost to DHBs			
	Net present value			
Other DHB costs	Net cost to DHBs			
Total	Total cost to DHBs			
	Net present value			

- Notes.
- Subsidy (gross) = forecast of spending on dabigatran at the proposed subsidy.
- Net cost to Schedule = forecast of change in total spending on pharmaceuticals listed on the Schedule compared with status quo.
- Total cost to DHBs = Net cost to the Schedule plus savings from reduction in warfarin monitoring costs and savings from reduction in warfarin/aspirin/rivaroxaban drugs costs and additional costs from increased dabigatran usage in hospital inpatients.
- All costs are expressed ex manufacturer, excluding GST.
- NPV is calculated over 5 years using an annual discount rate of 8%.
- Calculations in A390361.

EXECUTIVE SUMMARY

- Currently, warfarin is the preferred treatment in atrial fibrillation patients at intermediate to high risk of stroke. However it is labour intensive for clinicians and patients as it has a narrow therapeutic index requiring frequent blood test monitoring and associated dose adjustments. Under-anticoagulation and over-anticoagulation often occur creating stroke and bleeding risks. Due to these difficulties, a large proportion of patients are being treated with aspirin, which is less efficacious.
 - Direct thrombin and Factor Xa inhibitors are new classes of oral anticoagulants that do not require regular blood monitoring and are likely to replace warfarin internationally.
 - The proposal is to fund dabigatran (Pradaxa), a direct thrombin inhibitor. It is indicated for venous thromboembolism (VTE) prophylaxis following major orthopaedic surgery and stroke prevention in atrial fibrillation (AF).
 - Funding dabigatran would
 - provide a cheaper alternative to the currently funded oral treatment, rivaroxaban, for VTE prophylaxis following major orthopaedic surgery,
 - provide a more efficacious alternative to aspirin for patients with AF who can not use warfarin because of contraindication or difficulty in maintaining INRs within the therapeutic range,
 - provide an equally efficacious alternative to warfarin for patients with AF without the burden of the warfarin management and testing requirements,
 - have a cost per QALY of [REDACTED] for stroke prevention in AF although this only accounts for health related quality of life benefits and cost offsets – it does not include the benefit associated with the removal of the burden of the warfarin testing requirements: and,
 - be a cost to the Pharmaceutical Budget of approximately [REDACTED] and a cost to DHBs of [REDACTED] (5-year NPV, 8% discount rate).
 - provide a [REDACTED] discount on the list price, at which it would likely cost [REDACTED] over 5 years to provide the same access (provided the volume forecasts are correct).
- [REDACTED]
- PTAC considers open listing dabigatran to be acceptable – it also considers an implementation programme to be essential (the consultation responses also emphasis this).
 - We are proposing a significant implementation campaign. A particularly important part of this is the development of DHB guidance for managing bleeding. Should the Board approve the proposal we would work to have this guidance available by mid-June, or otherwise we propose delaying the listing.

Why Proposal Not Decided Under Delegated Authority

The proposal outlined in this Board paper has not been dealt with by the Chief Executive under delegated authority because the estimated Financial Impact (NPV) of this proposal is more than \$10,000,000 of the Pharmaceutical Budget. The Financial Impact (NPV) is calculated on the basis of the net present value of the proposed subsidy (ex-manufacturer exclusive of GST) over 5 years at a discount rate of 8% to be paid by the funder for the product(s) and the forecast demand, taking into account any effect of the decision on that demand, versus the status quo.

The Proposal

It is proposed that dabigatran (Pradaxa) 75mg, 110mg and 150mg capsules be listed in Section B and Part II of Section H of the Pharmaceutical Schedule without restriction and at a price and subsidy of \$148.00 for 60 tablets from 1 July 2011

An agreement, conditional upon consultation and Board approval, between Boehringer Ingelheim (NZ) Limited and PHARMAC (dated 1 April 2011) is attached as Appendix 1.

This agreement differs from a standard listing agreement as it:

- contains confidential rebates and agreed expenditure levels;
- contains subsidy and delisting protection until 30 June 2016; and,
- allows PHARMAC to change the packaging from a bottle to blister packs.

Estimate of the Effects of the Proposal

Clinical effects

VTE prophylaxis following major orthopaedic surgery

This proposal provides a cheaper and clinically similar oral treatment to the currently listed oral treatment rivaroxaban.

The clinical trials supporting dabigatran in VTE prophylaxis following total knee and hip replacements (RE-MOBILIZE, RE-MODEL and RE-NOVATE) found:

- dabigatran to be non-inferior to enoxaparin
- no significant differences in major bleeding events between dabigatran and enoxaparin

While there are no head-to-head clinical trials comparing dabigatran and rivaroxaban, the clinical trials comparing dabigatran with enoxaparin (RE-MOBILIZE, RE-MODEL and RE-NOVATE) had similar results to the clinical trials comparing rivaroxaban to enoxaparin (RECORD 1, 2, 3 and 4) – PTAC considers that dabigatran has the same or similar clinical effect as enoxaparin and rivaroxaban.

AF

In AF this proposal would provide:

- a more efficacious alternative to aspirin for patients with AF who cannot use warfarin because warfarin is contraindicated or because maintaining INRs within the therapeutic range is difficult; and,
- provide an equally efficacious alternative to warfarin for patients with AF without the burden of the warfarin testing requirements.

Although New Zealand and other international guidelines recommend long-term anticoagulant therapy with warfarin in patients with AF at intermediate and high risk of stroke (based on the Framingham or CHADS₂ risk stratification system), anticoagulation in AF is often suboptimal due to the difficulties and risks with warfarin therapy.

This is because the use of warfarin is complicated due to its narrow therapeutic range. 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 (odds of stroke doubled at an INR of 1.7) while over-anticoagulation can result in haemorrhage, including intracerebral haemorrhage (ICH). At INRs above 3.5, the relative odds of ICH is 4.6 when compared to INRs 2.0-3.0. Therefore, regular blood monitoring is required with warfarin therapy which frequently requires associated dose adjustments.

Due to the difficulties with warfarin administration, a significant proportion of patients with AF (namely patients with unstable INRs, elderly patients or patients living in rural areas) at intermediate or high risk of stroke are treated with aspirin instead. For this patient group, dabigatran is likely to offer increased efficacy. While there are no comparative studies between dabigatran and aspirin currently available the RE-LY trial (discussed below) found dabigatran to be as efficacious as warfarin and the BAFTA trial (Mant J, et al. Lancet 2007; 370: 493-503) which compared the efficacy of warfarin versus aspirin in AF found that warfarin resulted in an absolute risk reduction of 2% in the primary outcome (including 1.8% reduction in ischemic strokes) when compared to aspirin. While PTAC was concerned with the lack of direct comparative evidence in this regard it did consider that this patient group would possibly benefit the most from dabigatran.

For patients currently using warfarin dabigatran would provide an equally efficacious treatment without the burden of the warfarin testing requirements. The RE-LY trial compared warfarin therapy to dabigatran 110mg and 150mg administered twice daily for AF. For the primary outcome of stroke or systemic embolism, the 110mg dose of dabigatran resulted in an absolute risk reduction (ARR) of 0.16% and was found to be non-inferior to warfarin. The 150mg dose of dabigatran resulted in an ARR of 0.58% ($p < 0.001$) and was found to be statistically significantly superior to warfarin. The rate of major bleeding when the 110mg dose of dabigatran was administered twice daily was significantly less than for those administered warfarin (3.36% compared to 2.71%, $p = 0.003$). For those administered 150mg dabigatran twice daily, similar rates of major bleeding were observed when compared to warfarin (3.11% compared to 3.36%, $p = 0.31$). Both doses of dabigatran were associated with significantly lower rates of haemorrhagic strokes when compared to warfarin. PTAC considers warfarin and dabigatran to be equivalent.

Clinical issues with dabigatran

Although regular monitoring is not required with dabigatran due to its predictable pharmacokinetics, measuring the effects of dabigatran would be necessary when patients present with adverse effects such as bleeding. However, there is currently no direct monitoring test for dabigatran unlike INR levels for warfarin, but there are some tests that can be done to assess a patient's bleeding risk including:

- Ecarin clotting time (ECT) – this is the best method to assess bleeding risk.
- Thrombin Time and Activated Partial Thromboplastin Time (aPTT) – these are the most accessible qualitative methods for determining the presence or absence of an anticoagulant effect due to dabigatran.

There is also no specific antidote for dabigatran, unlike Vitamin K for warfarin. While this is not ideal it is not a unique problem – for example clopidogrel also has no antidote. In addition a number of measures that can be taken to reverse the anticoagulant effect of dabigatran, these include:

Mild bleeding	Drug discontinuation
Moderate-severe bleeding	Symptomatic treatment Mechanical compression Surgical intervention Fluid replacement and hemodynamic support Blood product transfusion Oral charcoal application Hemodialysis
Life-threatening bleeding	Recombinant factor VIIa or prothrombin complex concentrates (PCC) Charcoal filtration

While there are clinical risks associated with dabigatran, there are clinical risks associated with all pharmaceuticals. The alternative therapy, warfarin, is also associated with significant morbidity and mortality clinical risks due to its narrow therapeutic index. It also interacts with a large number of common medicines and foods, and clinical trials have shown that a majority of patients only have INRs in the therapeutic range approximately 60% of the time.

Cost of the products

The dabigatran listing price is significantly higher than that of alternative treatments. However, the cost is reduced through a confidential [REDACTED] rebate off the list price and an [REDACTED]

Relevant Period	[REDACTED]
1 July 2011 – 30 June 2012	[REDACTED]
1 July 2012 – 30 June 2013	[REDACTED]
1 July 2013 – 30 June 2014	[REDACTED]
Each subsequent 12 month period	[REDACTED]

The subsequent gross and net costs of the relevant products are shown in the following table:

Treatment	Gross cost	Net cost (post rebate)
Atrial fibrillation		
Dabigatran	\$1,800 p.a.	[REDACTED]
Warfarin	\$30 - \$60 ² p.a.	
Warfarin monitoring	\$255 p.a.	
Aspirin	\$5 p.a.	
VTE prophylaxis following major surgery		
Dabigatran	\$4.93 per day	[REDACTED]
Rivaroxaban	\$10.20 per day	[REDACTED]
Enoxaparin	\$5.20 per day ³	

¹ Based on applying forecast patient numbers to the [REDACTED]

² Range based on range of dose used.

³ Treatment duration dependant of surgery and clinician preference, < 40 days.

Cost-effectiveness

VTE prophylaxis following major orthopaedic surgery

Based on PTAC’s recommendations that dabigatran has similar efficacy as rivaroxaban and enoxaparin for this indication (see PTAC minutes below), funding dabigatran would be [REDACTED] given its lower price and subsidy.

AF

When current aspirin and warfarin patients are considered individually the cost-effectiveness of dabigatran is:

- Aspirin patients - [REDACTED]
- Warfarin patients - [REDACTED]

Given the high cost of dabigatran we considered only funding it for those who would gain the most benefit via Special Authority – these being patients who would use aspirin rather than warfarin - however both PTAC and the Cardiovascular Subcommittee consider that this would be impractical and that either it should be funded for all patients or not funded at all.

Combining the above groups, as per the proposal and PTAC’s advice, the average incremental cost per quality-adjusted life year (QALY) is [REDACTED]. There are a number of assumptions around this value with the most significant being what treatment the patients would use if dabigatran was not funded – we have assumed that 75% would be on warfarin and 25% would be on aspirin as follows:

Weight	Dabigatran compared to	Cost Per QALY	QALY gained per \$1 million invested
75%	Warfarin	[REDACTED]	[REDACTED]
25%	Aspirin	[REDACTED]	[REDACTED]
	Average	[REDACTED]	[REDACTED]

The key evidence for dabigatran is the phase III non-inferiority trial, RE-LY. The RE-LY trial was designed to show non-inferiority of dabigatran compared with warfarin. The trial reported that dabigatran 300 mg daily was superior to dose-adjusted warfarin; however PTAC and the Cardiovascular Subcommittee considered that, until further evidence becomes available, dabigatran should be considered therapeutically equivalent to warfarin. Therefore, compared with warfarin, dabigatran is expected to [REDACTED] not be associated with any QALY gains. This takes into account decreased warfarin monitoring costs. If dabigatran is assumed to be more effective than warfarin, the proposal becomes much more cost effective.

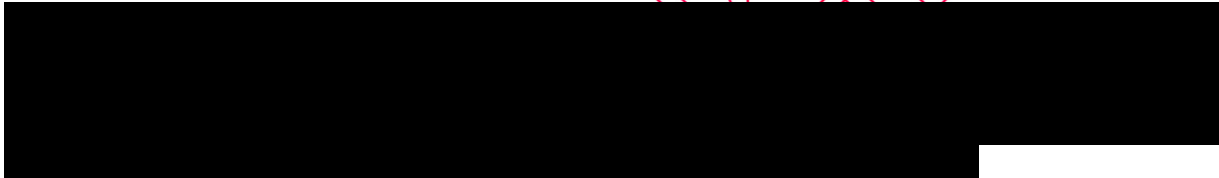
There was no evidence identified that compared dabigatran with aspirin, therefore an indirect comparison of the clinical evidence was made. The BAFTA trial that compares aspirin to warfarin was used.

Key inputs in the model included the reduction of 1.8% in ischemic stroke per annum, derived from the BAFTA trial. A key uncertainty in the comparison of dabigatran with aspirin is to what degree a reduction in risk of stroke reduces mortality. This is important as 84% of the estimated benefit is from increased life expectancy.

The results of the CUA are sensitive to changes in the:

- proportion of patients switching from warfarin or aspirin to dabigatran;
- reduction in overall mortality;
- QALY gain associated with dabigatran when compared with warfarin;
- reduction in risk of ischemic strokes; and
- cost of dabigatran.

Further information is in the attached Technology Assessment Report (TAR 165) - see Appendix 3 TAR 165 – Dabigatran in Atrial Fibrillation for the prevention of Stroke and Systemic embolism.



RELEASED
OFFICIAL INFORMATION

Budget impact

AF is the largest indication requiring long term anticoagulation and would make up the largest proportion of patients being treated with dabigatran. Based on [REDACTED], we estimate that there would be approximately [REDACTED] to [REDACTED] (PYE) patients eventually switching to dabigatran from warfarin and aspirin. Patients using dabigatran for VTE prophylaxis would make up a much smaller proportion with a shorter term of treatment.

The proposal is estimated to be a 5-year NPV cost of [REDACTED] to the Pharmaceutical Budget. This reduces to [REDACTED] to DHBs as a result of [REDACTED] in savings due to reduced warfarin drug monitoring as shown below. However, as above, should [REDACTED]

	2011/12	2012/13	2013/14	2014/15	2015/16	5-year NPV
VTE prophylaxis patient numbers (PYE) ¹	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
AF patient numbers (PYE) ¹	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total patient numbers (PYE)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Gross cost of proposal to Pharmaceutical Budget	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Offsets from rebates ²	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Drug cost offsets ³	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost of proposal to Pharmaceutical Budget⁴	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Warfarin monitoring cost offsets ⁵	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Increased inpatient drug costs to DHB hospitals ⁶	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost of proposal to DHBs⁷	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

1. Of the expected patients that will use dabigatran (derived from current [REDACTED] and NHI claims data) we anticipate an uptake rate of [REDACTED]
2. This includes a straight [REDACTED] rebate off community sales of dabigatran and the [REDACTED]
3. This includes reduction in warfarin, aspirin and rivaroxaban drug costs.
4. Net cost to Pharmaceutical Budget = Gross cost of proposal – Offsets from rebates - Drug cost offsets.
5. This includes cost of blood tests and clinician time needed for warfarin drug monitoring and assumes that all DHB's realise savings on lab tests from the start of 2011/12.
6. This takes into account possible increase in drug costs to hospitals if dabigatran used preferentially to warfarin or aspirin for hospital inpatients.
7. Net cost of proposal to DHBs = Net cost of proposal to Pharmaceutical Budget – Warfarin monitoring cost offsets – Increased inpatient drug costs to DHB hospitals

The patient numbers used to derive the above expenditure cost estimates assume that dabigatran would only be used in the approved indications. As dabigatran would be listed without Special Authority restriction, like all open listed drugs there would be a possibility that it would be used off-indication (for example for VTE treatment, VTE prophylaxis in non-orthopaedic indications and prosthetic valves).

[REDACTED]

[REDACTED]

PHARMAC Staff View

PHARMAC staff support this proposal for the following reasons:

An opportunity to improve anticoagulation management resulting in better clinical outcomes

New classes of medicines like dabigatran have been long awaited by clinicians and patients. As eluded to in the consultation responses, warfarin management is associated with significant clinical risks given its narrow therapeutic index. Over-anticoagulation is a risk for bleeding, the most severe being intracerebral haemorrhages whilst under-anticoagulation is a risk for ischaemic strokes. Frequent blood tests are also required to monitor its anticoagulant effect or INR followed by the requirement for dose adjustments. Due to all these issues, many at-risk patients are found to be unsuitable for warfarin therapy and are treated suboptimally with aspirin instead.

This proposal would improve the clinical outcomes for those patients treated with aspirin and it would remove the significant burden of the warfarin testing requirements for those that use warfarin.

[REDACTED]

Budget impact

[REDACTED]

[REDACTED]

Clinical issues and education

PTAC and a number of the consultation responses highlighted the need for significant education for clinicians as they would not have experience with this type of product and it has,

like all pharmaceuticals, issues that the clinician needs to be aware of. Having considered the advice and consultation responses it seems to us that the appropriate course of action would be to make the listing contingent on management of the patient safety issues (ie clinical guidance on how to manage dabigatran-associated bleeding) being addressed. As in our view the more general educational work could be provided at, or soon after, the listing date.

Therefore two important pieces of implementation work that we would perform prior to listing are:

1. Placing an advertisement in relevant publications such as NZ Doctor (29 June edition) stating that dabigatran will be funded and what sources of educational information will be made available and when this will occur – this will provide clinicians with the knowledge of where to source clinical information and when it will be available.
2. In conjunction with the Haematology Society of Australia & New Zealand (HSANZ) we would facilitate the development of anticoagulation guidance for managing bleeding episodes – we consider it important to ensure that guidance is in place prior to funding in the event that a patient is admitted to hospital. We note that if the guidance has not been developed prior to 12 June then we would delay the listing.

We have already performed a significant amount of this preparatory work. More detailed information regarding the implementation is included in the implementation section of this paper. However we are working closely with BPAC, the supplier, relevant Societies and clinicians to facilitate education at both the primary and secondary care levels.

We are not recommending delaying the proposal to ensure the in-depth and extended programme is fully developed because the general educational work is of an ongoing nature and it is our experience that once a decision is made and becomes public knowledge – such as through notification of the supplier, in this case Boehringer, aggressively market their product and providing 'education' - that prescriptions will start to be written and if there is a delay until funding then this causes significant sector disruption.

Background

Dabigatran and its Uses

Dabigatran is a direct thrombin inhibitor registered in New Zealand for the prevention of stroke, systemic embolism and reduction of vascular mortality in AF, as well as, VTE prophylaxis following major orthopaedic surgery.

The Dynamics of the Market for AF

Based on estimates by the New Zealand Guidelines Group, there are approximately 30,000 to 100,000 patients with AF in New Zealand.

The preferred treatment for stroke prevention in these patients is warfarin, although aspirin is used when warfarin is unsuitable.

The number of patients and yearly expenditure on these products in AF is shown below – this leaves a potentially significant number of patients not being treated (presumably they are at low risk).

Treatment	Patients	% patients	Expenditure
Asprin	8,000	26%	\$41,000
Warfarin	23,000	74%	\$1,400,000

The Dynamics of the Market for VTE prophylaxis following major orthopaedic surgery

Currently, the funded alternatives for VTE prophylaxis following major orthopaedic surgery include enoxaparin and rivaroxaban. However, enoxaparin is a subcutaneous injection whilst rivaroxaban is an oral treatment.

Current expenditure on these products is about [REDACTED] - enoxaparin accounts for [REDACTED] of this although rivaroxaban was only recently listed in December of last year.

Given that dabigatran is also an oral treatment if it is going to be used it is likely that it would compete for marketshare with rivaroxaban.

Other products in development and new indications

There are two classes of anticoagulants currently undergoing extensive clinical trials for various indications. These are Direct thrombin inhibitors and Factor Xa inhibitors and include a number of products at various stages of development as shown in the following table:

[REDACTED TABLE]

The number of indications for these products is likely to increase as clinical trials investigating their use in acute coronary syndrome, percutaneous coronary intervention, VTE treatment and VTE prophylaxis in other clinical conditions are currently being performed.

New anticoagulants currently in development

Drug class	Drug	Stage of development for AF
Factor Xa inhibitors	Rivaroxaban (Bayer)	[REDACTED]
	Apixaban (BMS/Pfizer)	[REDACTED]
	Betrixaban (Portola Pharmaceuticals/ Merck)	[REDACTED]
	Edoxaban (Daiichi-Sankyo)	[REDACTED]
Direct Thrombin Inhibitors	Ximelagatran (Astra Zeneca)	[REDACTED]
	Dabigatran etexilate (Boehringer)	[REDACTED]

International Prices for dabigatran

A comparison of international prices for dabigatran is outlined below.

Country	Source	Strength	Pack Size	Local Price	Exchange Rate	Price (\$NZ)
Proposal		75mg	60			\$148.00*
		110mg	60			\$148.00*
		150mg	60			\$148.00*
United Kingdom	BNF	75mg	60	£126.00	0.4666	\$240.03
		110mg	60	£126.00	0.4666	\$240.03
Australia	PBS	75mg	60	\$189.54	0.7772	\$243.87
		110mg	60	\$189.54	0.7772	\$243.87
US		75mg	60	\$202.50	0.7215	\$280.66
		150mg	60	\$202.50	0.7215	\$280.66

*The net price of dabigatran after confidential rebates is approximately [REDACTED]

Note: Prices are expressed ex manufacturer, excluding GST.

PTAC View

A complete compilation of the relevant PTAC and Cardiovascular Subcommittee meeting minutes are attached in Appendix 2. A summary of them are as follows:

Dabigatran Etextilate and Rivaroxaban for the Prevention of Venous Thromboembolic Events in Patients Undergoing Orthopaedic Surgery

- Dabigatran, rivaroxaban and enoxaparin have the same or similar clinical effect and could be listed in the same therapeutic subgroup for the purposes of reference pricing.
- Dabigatran be listed on the Discretionary Community Supply (DCS) list with a low priority following knee and hip orthopaedic surgery for a duration of up to 10 days and 35 days respectively.
- Rivaroxaban be listed for the treatment of venous thromboembolism prophylaxis after major orthopaedic surgery with a medium priority.

Dabigatran (Pradaxa) for stroke, systemic embolism, atrial fibrillation

October 2010 Cardiovascular Subcommittee minutes

The Subcommittee considered that the RELY trial showed that both doses of dabigatran were non-inferior to warfarin for the primary outcome with little difference in major bleeding. The Subcommittee noted that although the trial was a non-inferiority trial, the 300mg dabigatran dose was superior to warfarin for the primary outcome with an ARR of 0.58%.

The Subcommittee considered that dabigatran would remove the need for regular venepunctures and the difficulty with drug as well as food interactions with warfarin. The Subcommittee considered that the ease of use of dabigatran would increase the use of anticoagulation and probably reduce the burden of stroke to the health system in those poorly controlled on warfarin or on aspirin. However, the Subcommittee noted that there are risks with dabigatran therapy including a lack of long term outcome and adverse effect data, and no antidote for bleeding from dabigatran, unlike Vitamin K for warfarin. The Subcommittee considered that there would need to be some guidance provided to clinicians to mitigate and manage the bleeding risk if dabigatran is listed.

The Subcommittee considered that while dabigatran and warfarin were clinically equivalent dabigatran would make management of patients easier and would be an advantage for patients contraindicated or difficult to control with warfarin and are therefore on aspirin. The Subcommittee however noted that it had a much higher cost.

The Subcommittee recommended that dabigatran be listed on the Pharmaceutical Schedule with a medium priority. The Subcommittee considered that listing both strengths of dabigatran would be appropriate to allow for dose-adjustment in certain patient groups including those with renal impairment.

November 2010 PTAC minutes

The Committee recommended that dabigatran be funded with low priority for prevention of stroke, systemic embolism and reduction of vascular mortality in atrial fibrillation. The Committee considered that based on the RE-LY trial, the absolute risk reduction with dabigatran when compared with warfarin, although statistically significant, was very small (ARR 0.58%). The Committee also considered that the inability to monitor dabigatran therapy could mean that the first sign of over anticoagulation could be a major haemorrhage, especially in the elderly and those with renal impairment. There is also currently no antidote for dabigatran in the event of haemorrhage. The Committee noted that patients with a creatinine clearance of <30ml/min were excluded from the RE-LY trial. The Committee also considered that there are potentially significant drug interactions between dabigatran and p-glycoprotein inhibitors, with a risk of severe bleeding, and that possible interacting drugs are likely to include more than just verapamil, amiodarone and quinidine.

The Committee noted that the primary safety outcome of major bleeding in the RE-LY trial was lower with both dosages of dabigatran and was statistically significant for the 110mg dose. The Committee noted that the rate of gastrointestinal bleeding was significantly higher with the 150mg dabigatran dose than warfarin, but intracranial haemorrhage was significantly lower with both dosages of dabigatran. The incidence of haemorrhagic stroke was significantly lower for both dosages of dabigatran when compared with warfarin, but the incidence of myocardial infarction was significantly higher in the dabigatran groups. The Committee noted that the mortality rate from any cause was not statistically different between the three treatment arms.

The Committee considered that although one of the advantages of dabigatran is its ease of use, it is noteworthy that the rates of discontinuation in the RE-LY trial were about 5% higher with dabigatran when compared with warfarin. Dyspeptic symptoms may also be a significant issue in real life practice. The Committee also considered that, due to its short half-life (unlike warfarin), missing a dose of dabigatran could be associated with an increased risk of stroke.

The Committee considered that although clinical evidence is currently lacking, the patient group most likely to benefit from dabigatran would be the patients who are currently on aspirin for AF because warfarin is contraindicated or maintaining INRs within the therapeutic range is difficult.

The Committee considered that it would be difficult to restrict dabigatran use to certain subgroups of patients with atrial fibrillation without a significant risk of other patients with atrial fibrillation gaining access.

The Committee noted that although there are potential advantages of an oral anticoagulant like dabigatran that does not require regular monitoring, the main issue with dabigatran is its high cost and the risk of it being used in other patient groups beyond the funded indications.

February 2011 PTAC minutes

PTAC noted the recommendation by the Cardiovascular Subcommittee for dabigatran to be listed with medium priority for patients with atrial fibrillation. PTAC also noted that PHARMAC staff had received a commercial proposal for dabigatran to be listed without restriction on the Pharmaceutical Schedule at a [REDACTED] lower price than previously indicated. PTAC considered that it was appropriate to list dabigatran without restriction due to the more cost-effective price. PTAC also considered that educational support should be provided to clinicians when dabigatran is listed. PTAC considered that if dabigatran is listed without

restriction, a large proportion of patients on warfarin for atrial fibrillation would switch and it would also be used off-indication for conditions like prosthetic heart valves.

May 2011 Draft PTAC minutes

The Committee noted that PHARMAC had recently consulted on a proposal to fund dabigatran without Special Authority restriction. The Committee considered that listing dabigatran without restriction was appropriate considering the proposal resulted in a more cost-effective price for the medicine.

The Committee recommended that PHARMAC consider delaying the listing of dabigatran by a few months to allow for educational programmes to be implemented for prescribers prior to any listing as dabigatran is part of a new class of treatments and there is very little clinical experience with the product.

The Committee also recommended that dabigatran be included on the Intensive Medicines Monitoring Programme (IMMP) to enable safety monitoring and collection of data given it is a new treatment in New Zealand and worldwide.

RELEASED UNDER THE OFFICIAL INFORMATION ACT

Comments from Interested Parties

Section 49(a) of the New Zealand Public Health and Disability Services Act 2000 (the Act) requires PHARMAC to consult, when it considers appropriate to do so, on matters that relate to the management of pharmaceutical expenditure with any sections of the public, groups or individuals that, in the view of PHARMAC, may be affected by decisions on those matters.

Accordingly, a consultation letter was circulated on 8 April 2011 to all suppliers and other parties that, in the view of PHARMAC, may be affected by the recommendations contained in this paper. As the proposal would potentially affect many parties, the consultation letter was distributed widely to DHB hospitals, pharmacies, suppliers, interest groups, the Royal Australasian Colleges of General Practitioners, Physicians, Surgeons as well as their associated Societies. The consultation letter and all responses received by 29 April 2011 are attached as Appendix 4. Summaries of what PHARMAC staff believe are the significant matters raised in these responses are provided below. For the full response, please refer to Appendix 4.

Common themes raised during consultation

Improvements in anticoagulation management

[REDACTED] (~~Cardiovascular Subcommittee member~~) considers that dabigatran and similar products will revolutionise the management of patients with non-valvular AF by making life so much simpler for those who are on warfarin or ought to be but do not take it because of (non-bleeding) side-effects or the inability to meet the need for regular testing. He congratulates PHARMAC on reaching an agreement that would enable clinicians to offer dabigatran to New Zealanders.

[REDACTED] (*Taranaki Base Hospital*) considers that dabigatran would be a huge advance and suspects that most AF patients in the country would be on it within a few years. "Well done PHARMAC".

[REDACTED] (*Waitemata*) strongly supports the proposal and noted that the advent of dabigatran would follow its use elsewhere. He considers that dabigatran would increase the safety of anticoagulation in the many elderly AF patients who require INR testing at a great cost to the public system, and that it would also decrease the relatively common bleeding events as these patients overshoot their INR targets. He considers that dabigatran would be a large advance in cardiology therapeutics.

[REDACTED] (*NZ Blood*) supports the proposal as dabigatran is non-inferior to warfarin with a better safety profile. He considers that given the varied approaches to VTE prophylaxis post-hip and knee surgery, dabigatran would lead to more standardised management and better overall outcomes. He also noted that currently, the early phases of anticoagulation are often poorly controlled.

[REDACTED] (*University of Auckland*) supports the proposal to fund dabigatran especially for atrial fibrillation. He notes that the issue of warfarinising patients with atrial fibrillation in primary care has become a major "industry" that is very time consuming for practices and a considerable burden for patients. He also considers that there is a significant issue of safety which "burdens" GPs psychologically on a daily basis as INR results can be unpredictable and that warfarin management is an art rather than a science and to be able to dispense without testing would be a great relief.

[REDACTED] (*ProCare Health Limited*) strongly supports the proposal as it would improve anticoagulation treatment. He notes that there have been situations when practices have been unable to contact and inform patients within sufficient time to allow dose changes to occur, for example on weekends, public holidays, or when warfarin blood monitoring is being reported after hours. He also notes that dabigatran is associated with far fewer significant medicine interactions (e.g. erythromycin derivatives) compared to warfarin and unlike warfarin has no food interactions.

[REDACTED] (GP, [REDACTED]) supports the funding of dabigatran. He considers that as the evidence suggests that it is as effective as warfarin, there can only be benefit with significant overt and hidden savings. He also noted that patients will be pleased to avoid the inconvenience of painful blood tests, there is the avoidance of hospitalisation for elevated INR managements, and general practices spend considerable (unpaid) time in tracking down and advising patients of their INRs.

[REDACTED] (GP, [REDACTED]) noted that maintaining a therapeutic INR in patients who have English as a second language, who have frequent address changes, or who have their phones disconnected is a nightmare as well as a significant hazard, - and that in these patients he sometimes uses aspirin instead of warfarin as while it is less effective it is safer.

[REDACTED] (GP, [REDACTED]) considers that dabigatran would allow the safer management of people requiring anticoagulant therapy for AF in rural areas where access to regular INR testing is limited.

[REDACTED] (GP, [REDACTED]) fully supports the funding of dabigatran as a substitute for warfarin. She notes that many of her patients struggle to comply with regular warfarin testing, and that for some it is too difficult resulting in these patients being managed on aspirin and/or dipyridamole.

[REDACTED] (GP, [REDACTED]) supports the proposal as it would be a huge advantage given the current problems with managing patients on warfarin.

[REDACTED] (*Nurse Practitioner*) supports the proposal as it would greatly benefit her cardiac patients who require warfarin.

Improvements in health outcomes

[REDACTED] (*Stroke Foundation*) express their support for the proposal. They note that intracranial bleeding is the most feared complication of anticoagulant treatment, by both physicians and patients, and that dabigatran was associated with a highly significant reduction in this complication at both doses (relative risk compared with warfarin for 110mg = 0.31, $p < 0.001$; 150mg = 0.40, $p < 0.001$). They consider that this is an important advance over current treatment and while the 150 mg strength of dabigatran increases gastrointestinal bleeding compared with warfarin, this is regarded by patients and physicians as a less severe and more readily treatable adverse event than intracranial bleeding. They note that this perspective is echoed in the "Perspective" from the FDA team who licenced dabigatran only in the 150mg dose. They also consider that the simplicity of treatment initiation with dabigatran will result in additional savings in a hospital setting and would enable earlier discharge of patients for whom anticoagulation for the secondary prevention of AF-associated stroke is usually commenced in hospital. Finally they also note that while many hospitals have a haemostasis service to try to facilitate outpatient management of anticoagulation during warfarin initiation often this is not feasible in real life and it also has its own associated costs.

[REDACTED] (*Cardiologist, Middlemore*) is delighted with the proposal. He noted that patients often do not spend a great deal of time in the INR target range thus exposing themselves either to a loss of effect or the danger of complications and considers that a fixed dose regimen that does not require monitoring would be a huge step forward.

[REDACTED] strongly support the proposal.

Need for educational support

[REDACTED] (*Cardiovascular Subcommittee member*) supports the proposed funding of dabigatran. He notes that he has been giving his private patients with AF the option of dabigatran for several months and reports that almost everyone opts for dabigatran once the risks and benefits are explained. He concludes that he is in favour of it being widely available without Special Authority if appropriate education is undertaken.

[REDACTED] (*Cardiovascular Subcommittee member*) considers that funding will be well received in primary care. He considers that education for GPs will be needed including reminders on indications and risk scoring systems, and that the New Zealand Guidelines Group will need to consider updating their guidelines.

[REDACTED] (*Cardiovascular Subcommittee member*) considers that there is a need to educate clinicians about how to manage uncontrolled bleeding whilst on dabigatran and on which patients dabigatran should not be used for (e.g patients with mechanical valves). He also considers that clinical practices could be encouraged to audit their registers to identify patients who are not on warfarin and who could benefit from dabigatran.

Stroke Foundation

[REDACTED] consider that the introduction of dabigatran should be accompanied by adequate education to both primary and secondary care physicians about its appropriate use and that this should include dosing guidelines, thresholds for starting anticoagulation, managing gastrointestinal side-effects, drug interactions, management of bleeding episodes and management of dabigatran during acute and elective surgery. They note that the [REDACTED] is eager to be involved with this process.

Heart Rhythm New Zealand

[REDACTED] support the proposal and hope to be able to contribute to clarifying the indications and providing primary care guidelines for physicians who treat patients with AF.

Waikato

[REDACTED] prefers access to dabigatran to be more restricted initially as there is a need for a reversal plan to be formulated, like that for warfarin, and to be available in emergency departments before patients are offered the drug. She notes that studies have indicated that recombinant factor VIIa and Prothrombinex Complex Concentrate (PCC) are potential reversal agents and that the anticoagulant activity of dabigatran can be measured through ecarin times but pathology labs would need to be notified early so that they can be prepare to process more of these tests.

PHARMAC staff note: Under the provisional agreement with Boehringer, dabigatran would be open listed without Special Authority restriction. The consultation responses and feedback from PTAC and the Cardiovascular Subcommittee consider that the provision of information and education to prescribers is important to limit any safety risks. This is also the view of other clinical groups which we have informally contacted including the Ministry of Health's Haematology Working Group, the Cardiac Society and the Stroke Foundation. Work has begun on the implementation programme and the details are included in the Implementation" section below. In educating prescribers we will address issues around indications, dosing, drug interactions, managing side effects such as bleeding and measuring the anticoagulant effect. The proposal has also been discussed with the District Health Board's Service Improvement Group (DHB SIG) to facilitate forward planning of future anticoagulation services.

The safety of dabigatran given the potential side effects and the absence of direct monitoring tests or direct antidotes

[REDACTED] (NZ Blood) states that although initial data indicates that the risk for adverse bleeding events with dabigatran is not worse than warfarin, there is no antidote for an immediate correction of the anticoagulant effect with dabigatran which is in contrast to warfarin where Vitamin K and Prothrombin Complex Concentrate (PCC) corrects bleeding within 3-4 hours of onset. He considers that with dabigatran, a range of methods (including large doses of PCC) which are yet to be fully known would need to be used and that prescribers would need to be educated about this issue. Despite this risk with dabigatran, he considers that it should be noted that there is currently a significant death rate and severe adverse outcomes from bleeding due to warfarin and that only long-term experience will provide the required information to determine whether dabigatran or warfarin is better in this respect.

[REDACTED] Palmerston North

[REDACTED] considers that awareness needs to be raised among clinicians to develop protocols to manage dabigatran associated bleeding and treatment before and after surgery. He notes that recombinant factor VIIa has been used to control bleeding but that this is a considerable cost, the dosage is not yet established and that there are no standardised laboratory tests to evaluate the level of anticoagulation with dabigatran. He also notes that the RE-LY study showed an increased risk of myocardial infarction with dabigatran, although upon re-evaluation the finding was found to be erroneous, and that this is consistent with ximelagatran, which is also showed this risk and is also a direct thrombin inhibitor. He considered that if the proposal is approved, it would be a good opportunity to set up a surveillance program of patients switching to dabigatran to monitor any adverse outcomes.

[REDACTED] (Southland Hospital Drugs and Therapeutics Committee) regards the proposal as forward thinking but highlights potential issues as dabigatran not being a direct substitute for warfarin. He notes that the trial population excluded some populations who may be prescribed it in real life – younger patients and patients with renal impairment – and that as the CHADS-2 scoring system was not used in the trial, there is some uncertainty as to what risk scoring system would be appropriate. He also noted that there is uncertainty around the dose level and that there is a lack of evidence that dabigatran is indeed superior to aspirin. Finally he notes that the datasheet states that dosage adjustments are required in orthopaedic patients taking amiodarone, quinidine or verapamil but that dose adjustments are not required in AF and considers that the rationale and evidence for this discrepancy needs to be made clear.

[REDACTED] (Auckland University) supports the proposal to fund this potentially useful new agent but highlights the need for PHARMAC to undertake a

programme of education to promote responsible and informed prescribing by clinicians as dabigatran is not suitable for everyone. He notes that there is evidence that warfarin management can be improved using anticoagulant management services and considers that while Special Authority restrictions are burdensome to clinicians, they should be applied on clinical grounds if necessary to restrict dabigatran to those most likely to benefit from it. He notes that 40% of patients in the RE-LY trial were taking aspirin in addition to warfarin which would over-estimate dabigatran's safety advantage in terms of bleeding outcomes and that the rate of discontinuation was higher with dabigatran which could result in non-adherence with adverse consequences given its short half-life. He questions whether it might be better for dabigatran to be listed on the DCS list for orthopaedic indications as per PTAC's original recommendation.

[REDACTED] (*Pharmaceutical Society NZ*) considered that open listing dabigatran could be interpreted by GPs as a safer and more convenient anticoagulant than warfarin. He noted that there is considerable potential for significant drug interactions which is difficult to predict, unable to be clearly monitored and any toxicity is unable to be treated. He also noted that the datasheet provides understated and incomplete information on potential drug interactions and considered that this may result in pharmacists finding it difficult to identify potential issues.

PHARMAC staff note: Warfarin treatment is not without its clinical risks. Although its effects can be monitored through INR levels, many patients have labile INRs which put them at risk of adverse effects due to the drugs narrow therapeutic index. Although not direct measures, the anticoagulant effect or bleeding risk with dabigatran can be predicted through tests like the ecarin clotting time (ECT), thrombin time and activated partial thromboplastin time (aPTT). Although Vitamin K is a direct antidote for warfarin, prothrombinex complex concentrate (PCC) is still required during episodes of severe bleeding and may not be effective in those scenarios. Bleeding episodes with dabigatran can be managed through treatment cessation (given its relatively short half-life), PCC, Factor VIIa infusions and it is also dialyzable if required. The RE-LY study also indicated that dabigatran was associated with significantly less intracerebral haemorrhages (the most significant bleeding event with warfarin) when compared with warfarin in AF. As highlighted by other responses, education at the primary care level and within hospitals would help address the clinical risks associated with this proposal – see PHARMAC staff note above. We note that the specific issues highlighted above in regards to the dabigatran datasheet have been communicated to the supplier. Also, dabigatran would not suit a DCS listing, even for the orthopaedic indication as it is a long-term community treatment and PTAC only initially recommended this as at the time the only access to low molecular weight heparin was via DCS – since then enoxaparin has been listed on the Pharmaceutical Schedule.

[REDACTED] (*Hutt Hospital*) foresees a significant problem if a patient has not been compliant with dabigatran and presents with a cerebral infarction as the patient will not be able to be thrombolysed as their level of anticoagulation will be unknown. He therefore considers that dabigatran should be reserved for those with labile INRs.

PHARMAC staff note: We understand that there are coagulation tests which could determine their level of anticoagulation. When we develop the guidance for bleeding we will also be developing guidance for coagulation testing.

Inappropriate prescribing by clinicians

[REDACTED] (*Cardiovascular Subcommittee member*) supports the proposal but considers that clinicians may use dabigatran in areas where it has

not been trialled or approved such as for mechanical valves, rheumatic heart disease and those with marginal risk scores.

Palmerston North

considers that limitations exist on the prescribing of dabigatran and that adherence to these might be best achieved through a Special Authority process as otherwise clinicians may believe that dabigatran can replace warfarin in all conditions. He notes that although data is accumulating for the use of dabigatran in the management of deep vein thromboses and pulmonary embolisms, there are no trials for dabigatran in heart valve patients and as the drug has a different mode of action to warfarin we should be cautious about accepting that it has the same therapeutic benefit in all circumstances. Finally he noted that when the FDA approved dabigatran for AF they only approved the 150mg dose and he believes that it would be sensible to follow the FDA lead.

PHARMAC staff note: These issues are addressed in the PHARMAC staff note under 'Need for educational support' heading above.

Cost to the Pharmaceutical Schedule and to DHBs

Tauranga and Whakatane considers that clinicians will be very pleased with the proposal to list dabigatran but that there needs to be an assessment on the impact on inpatient medication costs if dabigatran is used preferentially to warfarin.

PHARMAC staff note: The preferential use of dabigatran over warfarin in inpatients would cost hospitals approximately (5-year NPV, 8% discount rate) after confidential rebates and taking into account a reduction in inpatient warfarin monitoring costs. The proposal would however result in greater savings to DHBs in the long term as warfarin monitoring services are redefined.

Roche Diagnostics considers that better warfarin management through Patient or Pharmacy-Led Services could improve outcomes with warfarin therapy and prove more cost-effective than dabigatran. It notes that the annual costs of warfarin management through Pharmacy-Led and Patient-Self monitoring programmes are \$580 and \$570 respectively versus \$1800 for dabigatran.

PHARMAC staff note: After taking into account confidential rebates, the average drug cost for dabigatran per patient per year would be approximately. This is further reduced to per patient per year after taking into account warfarin monitoring cost which is about the same level as warfarin management through Pharmacy-Led and Patient-Self monitoring programmes. Although we note that we estimate the cost of warfarin monitoring to be less than estimate; most of the difference is due to the frequency of monitoring costs; where estimate of 1.7 tests is based on a relatively small Auckland based study and PHARMAC estimates a test every 6 weeks based on national lab test data.

The future availability of other drugs in these classes of treatment

Cardiovascular Subcommittee member) supports this proposal but is concerned that competitor drugs, one or more of which may eventually prove to have advantages over dabigatran, may be locked out of the market for some time.

[REDACTED] (NZ Blood) noted that a range of oral anticoagulants similar to dabigatran are in development and considers that the length of the subsidy and delisting protection period may merit reconsideration as a competitive market is likely to develop in the near future.

Bayer NZ [REDACTED] states that there will be benefit of having more than one agent available due to the heterogenous nature of patients. It considered that this proposal would significantly impact on the current listing of [REDACTED]

[REDACTED]

PHARMAC staff note: [REDACTED]

[REDACTED]

[REDACTED]

We note that the agreement with [REDACTED] does not prevent PHARMAC from listing another agent, and they were consulted on this proposal. [REDACTED]

[REDACTED]

it or transitioned to it, what are the benefits and risks, what side-effects should be closely monitored and when should treatment be stopped;

- A June article in the Best Practice Journal introducing dabigatran, summarising the clinical trial evidence and discussing its role in AF.
- An August article in the Best Practice Journal illustrating the advantages and disadvantages of the current available therapies (warfarin, aspirin, dipyridamole, clopidogrel, prasugrel, dabigatran and rivaroxaban) in AF, myocardial infarction and stroke.
- The Best Practice Journal articles may be complemented by additional education through clinical facilitators, to be managed by Best Practice Advocacy Centre (BPAC);
- Educational interactive programme on Sky TV for clinicians (as conducted for the changes to Special foods);
- Communication with DHB hospitals regarding the need for the development of treatment protocols for dabigatran and the potential to scale down warfarin monitoring programmes over-time.
- Work with the supplier to coordinate implementation efforts and potentially add dabigatran to the Intensive Medicines Monitoring Programme (IMMP).
- Inform pathology labs to enable them to prepare for potentially more ecarin time testing.

Appendices

Appendix 1: Provisional agreement between Boehringer Ingelheim (NZ) Limited and PHARMAC (dated 1 April 2011).

Appendix 2: PTAC and Cardiovascular Subcommittee minutes

Appendix 3: TAR 105 – Dabigatran in Atrial Fibrillation for the prevention of Stroke and Systemic Embolism

Appendix 4: Consultation letter and responses

Decision Criteria

Set out below is PHARMAC staff's assessment of the application of the decision criteria in section 2.2 of the Operating Policies and Procedures. This assessment is intended for discussion purposes, is not necessarily exhaustive and is not a substitute for the analysis contained in the paper. The Board is not bound to accept PHARMAC staff's assessment of the application under the decision criteria and may attribute different weightings to each of the criteria from those attributed by PHARMAC staff.

1. *The health needs of all eligible people within New Zealand;*

The patient group most likely to benefit from dabigatran would be the patients who are currently treated suboptimally with aspirin for AF because warfarin is contraindicated or maintaining INRs within the therapeutic range is difficult. Currently there are 8,000 patients with AF using aspirin – an unknown proportion of these would be moderate to high risk and on aspirin because warfarin is not appropriate - advice from the Cardiovascular Subcommittee of PTAC suggests this proportion could be about 60%.

2. *The particular health needs of Maori and Pacific peoples;*

There is a higher risk of stroke and AF in Maori and Pacific peoples, therefore this proposal would particularly help address that health need.

3. *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;*

This proposal would provide more convenient access to an oral anticoagulant for VTE prophylaxis following major orthopaedic surgery.

Warfarin is currently considered the standard treatment for patients with AF at risk of stroke. However, because of its narrow therapeutic index, need for frequent blood tests with associated dose changes, many patients cannot be managed on it and are treated suboptimally with aspirin instead. This puts them at risk of ischaemic strokes and the associated morbidity and mortality.

4. *The clinical benefits and risks of pharmaceuticals;*

This proposal would improve VTE prophylaxis following major orthopaedic surgery by improving access, resulting in lower risks of venous thromboembolic events. In AF, this proposal would provide another treatment option. It is likely to result in improved clinical outcomes for patients with AF currently treated suboptimally with aspirin. The clinical risks of this proposal include off-indication prescribing and risks due to the lack of a direct monitoring test and a direct antidote. These clinical risks can be reduced through the education and dissemination of information to health professionals and patients.

5. *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;*

This proposal would be [REDACTED] for VTE prophylaxis following major orthopaedic surgery. The incremental cost per quality-adjusted life year (QALY) of a dabigatran compared with warfarin or aspirin for the prevention of ischemic stroke in atrial fibrillation was estimated to be [REDACTED]

6. *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule;*

This proposal is estimated to be a cost of [REDACTED] (5-year NPV, 8% discount rate) to the Pharmaceutical Budget. After taking into account offsets from warfarin drug

monitoring of approximately [REDACTED], this proposal would be a cost of [REDACTED] (5-year NPV, 8% discount rate) to DHBS.

7. *The direct cost to health service users;*

This proposal would provide fully fund dabigatran for patients, therefore there would be no need for them to pay for it themselves.

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*

Reducing the incidence and impact of cardiovascular disease is a Government priority for health funding.

9. *Such other criteria as PHARMAC thinks fit.*

No other criteria are relevant to assessing this proposal

RELEASED UNDER THE
OFFICIAL INFORMATION ACT

CHECKLIST FOR BOARD PAPERS

Paper: Dabigatran for Atrial Fibrillation and Orthopaedics

Date of Board Meeting: May 2011

Consultation:

The following parties were consulted with during the development of this paper.

Party	Consulted	Comments
Minister of Health	<input type="checkbox"/>	<input type="checkbox"/>
Ministry of Health	<input type="checkbox"/>	<input type="checkbox"/>
DHBs	<input type="checkbox"/>	<input type="checkbox"/>
PTAC	<input type="checkbox"/>	<input type="checkbox"/>
Consumer Advisory Committee	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Affected health professionals (refer to attached distribution list)	<input type="checkbox"/>	<input type="checkbox"/>
Affected patient/consumer groups (refer to attached distribution list)	<input type="checkbox"/>	<input type="checkbox"/>
Affected suppliers (refer to attached distribution list)	<input type="checkbox"/>	<input type="checkbox"/>
Other affected public, groups and/or individuals (specify)	<input type="checkbox"/>	<input type="checkbox"/>

The Author(s) confirm that appropriate processes were followed for the development of this paper, including appropriate consultation and consideration of consultation responses.

Principal Author: [REDACTED]

Other Authors: [REDACTED]

Reviewer(s): Steffan Crausaz
[REDACTED]

Approved: Matthew Brougham
Chief Executive