

PUBLIC SUMMARY DOCUMENT

Product: Dabigatran etexilate, capsules, 110 mg and 150 mg (as mesilate), Pradaxa®

Sponsor: Boehringer Ingelheim Pty Ltd

Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an extension to the current Authority Required listing to include the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (NVAF) who are at moderate to high risk of developing stroke or systemic embolism, who meet certain criteria. The submission requested an Authority Required (STREAMLINED) listing for this indication.

2. Background

The PBAC had not previously considered dabigatran for this indication.

Dabigatran etexilate capsules, 75 mg and 110 mg have been PBS listed since 1 April 2010 for the prevention of venous thromboembolism in a patient undergoing total hip or total knee replacement.

3. Registration Status

Dabigatran etexilate was TGA registered on 24 November 2008 for the prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement).

As at 29 April 2011, dabigatran etexilate TGA registered indications were extended to include for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)

Prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation who are at a moderate-to-high risk of developing stroke or systemic embolism as evidenced by one or more of the following risk factors:

Age \geq 75 years;

Hypertension;

Diabetes mellitus;

Heart failure or left ventricular dysfunction (ejection fraction < 40%) or a history of coronary artery disease;

Previous stroke or transient ischaemic attack or systemic embolism.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Atrial fibrillation (AF) is a cardiac arrhythmia characterised by uncoordinated atrial activation with consequent deterioration of mechanical function. The disturbed atrial and ventricular activation causes the stoppage of blood flow which may lead to thrombus clot formation, increasing the risk of stroke and other thromboembolic events.

AF is the most common form of arrhythmia and affects approximately 2% of the general population. The prevalence of AF rises with age, increasing to around 15% in those aged 80 years and above.

Non-valvular atrial fibrillation (NVAf) is a significant risk factor for thromboembolic events, particularly ischaemic stroke (IS).

The submission proposed that the place in therapy of dabigatran is as an alternative to adjusted-dose warfarin and aspirin as a first line treatment for the prevention of stroke or systemic embolism in moderate-to-high risk patients with NVAf.

6. Comparator

The submission nominated adjusted-dose warfarin and aspirin as the main comparators, which the PBAC considered to be appropriate.

7. Clinical Trials

The submission presented one randomised trial comparing dabigatran 150 mg twice daily (bd) and 110 mg bd with adjusted-dose warfarin in patients with NVAf (the RE-LY trial). The submission also presented six randomised controlled trials comparing adjusted-dose warfarin and aspirin to inform an indirect comparison between dabigatran and aspirin, using adjusted-dose warfarin as the common reference.

The trials published at the time of submission are presented in the table below:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Dabigatran 110 mg & 150 mg vs adjusted-dose warfarin		
RE-LY BI 1160.26		
Connolly S et al	Dabigatran versus warfarin in patients with atrial fibrillation.	New England Journal of Medicine 2009;361(12):1139-1151
Connolly S et al	Newly Identified Events in the RE-LY Trial	New England Journal of Medicine 2010;363(19):1875-1876
Wallentin L et al	Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the-RE-LY trial	Lancet 2010; 307;7945:975-983
Indirect comparison: adjusted-dose warfarin as common reference		
Adjusted-dose warfarin vs aspirin		
AFASAK I Petersen P et al	Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study.	Lancet 1989; 1:175-179.
Petersen P et al	Prevention of stroke in atrial fibrillation. (to the editor)	New England Journal of Medicine 1990; 323:482.

AFASAK II Gulløv AL et al	Fixed mini-dose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study.	Archives of Internal Medicine 1998. 158: 1513-1521.
Gulløv AL et al	Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation.	Archives of Internal Medicine 1999. 159: 1322-1328.
BAFTA Mant J et al	Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study; BAFTA): a randomised controlled trial.	Lancet 2007. 370: 493-503.
Chinese ATAFS Hu D et al	The randomized study of efficiency and safety of antithrombotic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin.	Zhonghua Xin Xue Guan Bing Za Zhi 2006. 34: 295-298.
SPAF II	Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study.	Lancet 1991. 343: 687-691.
WASPO Rash A et al	A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO).	Age and Ageing 2007. 36: 151-156.

8. Results of Trials

The results for the primary outcome of RE-LY, stroke/SEE are summarised below.

Non-inferiority of both dabigatran doses (110 mg bd and 150 mg bd) compared to adjusted-dose warfarin was demonstrated in the RE-LY trial for the primary efficacy outcome, based on non-inferiority thresholds of 1.46 and 1.38: The hazard ratio (HR) for dabigatran 110 mg bd = 0.90 (95% CI 0.74, 1.10) and for dabigatran 150 mg bd = 0.65 (95% CI 0.52, 0.81). Dabigatran 150 mg bd was also demonstrated to be superior to adjusted-dose warfarin for the primary endpoint of stroke/SEE, with a hazard ratio of 0.65 (95% CI 0.52, 0.81).

The mean time in therapeutic range (TTR) for patients enrolled from different countries in the RE-LY trial, for warfarin at different levels of international normalised ratio (INR) control (2-3) (Wallentin 2010) indicated that patients enrolled in Australian sites had a mean time in therapeutic range for warfarin of 74% based on a small number of patients.

The PBAC noted that published studies and an unpublished survey suggested that the time spent in target INR range varies between 50.4% and 68% in Australia.

The results for patients enrolled in centres with rates of centres mean time in therapeutic range (cTTR) >72.6%, compared with those reported in the ITT population are summarised in the following table:

Outcome	Hazard ratio (95% CI) cf with adjusted-dose warfarin			
	ITT (reported in submission/ used in model)		cTTR >72.6% (Australian patients in RE-LY had cTTR of 74%)	
	Dabigatran110	Dabigatran 150	Dabigatran	Dabigatran

			110	150
Stroke and systemic embolism ^a	0.90 (0.74, 1.10)	0.65 (0.52, 0.81)	0.92 (0.59, 1.45)	0.95 (0.61, 1.48)
Non-haemorrhagic stroke and systemic embolism	NR	NR	1.13 (0.69, 1.87)	1.21 (0.74, 1.98)
Intracranial bleeding ^b	0.30 (0.19, 0.45)	0.41 (0.28, 0.60)	0.27 (0.11, 0.66)	0.39 (0.18, 0.84)
Major bleeding	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)	0.90 (0.67, 1.21)	1.16 (0.88, 1.54)
Major gastrointestinal bleeding	NR	NR	1.46 (0.89, 2.41)	2.00 (1.25, 3.21)
Total bleeding ^b	0.78 (0.73, 0.83)	0.91 (0.85, 0.96)	0.84 (0.74, 0.95)	1.00 (0.89, 1.12)
Stroke, SEE, PE, MI, death and major bleeding	0.92 (0.84, 1.01)	0.90 (0.82, 0.99)	1.07 (0.87, 1.30)	1.11 (0.91, 1.35)
Stroke, SEE, PE, MI and CV death	NR	NR	1.27 (0.97, 1.67)	1.19 (0.90, 1.57)
Non-haemorrhagic stroke, SEE, PE, MI and CV death	NR	NR	1.29 (1.01, 1.64)	1.17 (0.91, 1.50)
Total death	0.90 (0.79, 1.03)	0.88 (0.77, 1.00)	1.18 (0.89, 1.57)	1.08 (0.81, 1.44)

SEE=systemic embolism; PE=pulmonary embolism; MI=myocardial infarction; CV=cardiovascular, NR=not reported

^a primary outcome

^b adjudicated events reported for ITT

In the ITT population, superiority was demonstrated for dabigatran 150 mg strength in reduction of stroke/systemic embolism (composite primary outcome), ischaemic stroke, haemorrhagic stroke, intracranial bleeding and death, although the latter was not quite statistically significant (HR 0.88, 95% CI 0.77, 1.00). For patients in centres with a mean time in therapeutic range (cTTR) >72.6% with adjusted-dose warfarin, the results demonstrated no statistically significant differences in the primary outcome of stroke/SEE in a post-hoc analysis.

The results for stroke/SEE reported in the aspirin trials and an indirect comparison with dabigatran showed that when all aspirin trials are considered, no statistically significant difference between adjusted-dose warfarin and aspirin was observed. However, excluding AFASAK II, a trial that was prematurely terminated, the results indicated that adjusted-dose warfarin is statistically significantly better than aspirin in preventing stroke/SEE.

Dabigatran and adjusted-dose warfarin are both associated with an increased risk of bleeding. Dabigatran is also associated with gastric adverse events.

9. Clinical Claim

The submission described dabigatran as superior in terms of comparative effectiveness and superior in terms of comparative safety over adjusted-dose warfarin. The PBAC accepted this claim, *see Recommendation and Reasons*.

The submission described dabigatran as superior in terms of comparative effectiveness and superior in terms of comparative safety over aspirin. The PBAC agreed that the indirect comparison demonstrated that dabigatran is more effective than aspirin but is likely to cause more bleeding.

10. Economic Analysis

The submission presented a modelled economic evaluation.

The base case assumed that dabigatran 150 mg and 110 mg are used 50:50 and that the comparators (adjusted-dose warfarin and aspirin) are also used 50:50.

The results of the economic evaluation, using total RE-LY data, produced a base case incremental cost/extra QALY over lifetime of less than \$15,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated by the submission to be greater than 200,000 in Year 5.

The financial cost/year to the PBS was estimated by the submission to be greater than \$100 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended the listing of dabigatran 150 mg and an extension to the listing of dabigatran 110 mg for the prevention of stroke or systemic embolism in moderate-to-high risk patients with non-valvular atrial fibrillation on the basis of acceptable cost effectiveness. Based on the high incidence of atrial fibrillation and the financial estimates in the submission over the first four years of listing, the Committee noted that the opportunity cost to the Commonwealth of listing dabigatran would be significant.

The requested restriction was considered to be consistent with the subjects enrolled in the main clinical trial (the RE-LY trial) and therefore appropriate. Although Medicare Australia would not be able to enforce compliance with the risk factors under the requested 'streamlined' authority, it would need to increase its workforce substantially to deal with the number of telephone requests, if listed as 'Authority Required'.

The PBAC noted that a number of patients who are reluctant to take warfarin because of the stringent monitoring requirements and interactions with other drugs and foods, but who should be taking oral anticoagulation, would now be treated with dabigatran and this would likely lead to additional benefits and costs not measured in the trial. The listing of dabigatran may also result in patients at low risk currently managed on aspirin or no treatment being unnecessarily transferred to dabigatran at a much higher cost.

The PBAC considered the comparators in the submission, adjusted-dose warfarin and aspirin, to be appropriate.

The PBAC noted that the RE-LY trial had been designed to test the non-inferiority of dabigatran 150 mg twice daily and 110 mg twice daily compared with adjusted-dose warfarin. However, the results of the trial suggested that although dabigatran 110 mg bd was non-inferior to adjusted-dose warfarin, dabigatran 150 mg bd was both non-inferior and superior to adjusted-dose warfarin. In the ITT population, superiority was demonstrated for the 150 mg strength in reduction of stroke/systemic embolism (composite primary outcome), ischemic stroke, haemorrhagic stroke, intracranial bleeding and death, although the latter was

not quite statistically significant (HR 0.88, 95% CI 0.77, 1.00). For patients in centres with a mean time in therapeutic range (cTTR) >72.6% with warfarin, the results demonstrated no statistically significant differences in the primary outcome of stroke/SEE. The PBAC noted that this sub-group included Australia, where the cTTR was measured in the RE-LY trial as 74% (refer to “Results of Trials”). However, the PBAC also noted that published studies and an unpublished survey suggested that the time spent in target INR range varies between 50.4% and 68% in Australia.

The PBAC also accepted that dabigatran is of similar overall safety to adjusted-dose warfarin, i.e. superior in terms of life-threatening and minor bleeds and inferior in terms of gastrointestinal adverse events. The PBAC noted reduced intracranial bleeding with dabigatran, an important benefit for patients.

However, although dabigatran 150 mg twice daily was superior to adjusted-dose warfarin in the RE-LY ITT population, this superiority may or may not be reflected in the Australian population, depending on the compliance of the patients prescribed daily warfarin and how compliant they might be with dabigatran twice daily. Further, the effectiveness of dabigatran in patients who are not fully compliant is unknown, but given its pharmacology is highly likely to be less than demonstrated in the RE-LY trial.

However, overall, the PBAC relied on the ITT results for both arms of the trial when forming its clinical conclusion that dabigatran is superior to warfarin and based its recommendation to list dabigatran on that analytical approach. Although the results for dabigatran 110 mg bd did not demonstrate superiority over adjusted-dose warfarin in the ITT population, the PBAC considered that this dose would be reserved for patients with renal insufficiency, in whom the lower dose would be highly likely to result in similar benefits over warfarin to dabigatran 150 mg bd in patients without renal impairment. The PBAC also agreed that the indirect comparison demonstrated that dabigatran is more effective than aspirin but is likely to cause more bleeding.

The results of the modelled economic evaluation were considered robust and remained within an acceptable range under sensitivity analysis, unless the duration of the model was reduced to 5 or 10 years, which the PBAC acknowledged was unreasonable. The Committee agreed that a duration of 20 years was reasonable for which the base case increased slightly per QALY. Issues were identified with non-significant point estimates being used in the model, but the PBAC noted that removal of these actually reduced the ICERs. Issues were also noted about the disutilities applied in the model, but the model was not found to be sensitive to these.

The PBAC considered the predicted utilisation of dabigatran in the submission may be underestimated, particularly if lower risk patients are prescribed the drug. The financial implications were predicted to be greater than \$100 million in Year 5, although there would be some savings to the MBS with a reduction in INR testing.

The PBAC recommended that dabigatran etexilate is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements as a shared care model.

Recommendation:

DABIGATRAN ETEXILATE, capsule, 150 mg (as mesilate)

Restriction: Authority Required (STREAMLINED)
Prevention of stroke or systemic embolism in a patient with non-valvular atrial fibrillation who are at moderate-to-high risk of developing stroke or systemic embolism as evidenced by one or more of the following risk factors:

- i) Age 75 years or older;
- ii) Hypertension;
- iii) Diabetes mellitus;
- iv) Heart failure or left ventricular dysfunction (ejection fraction less than 40%) or history of coronary artery disease;
- v) Previous stroke or transient ischaemic attack or systemic embolism.

NOTE

No applications for increased maximum quantities will be authorised.

Shared Care Model

For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.

Max qty: 60
Repeats: 5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Boehringer Ingelheim welcomes the recommendation of the PBAC and looks forward to the availability of dabigatran on the PBS for Australians with non-valvular atrial fibrillation at moderate-to-high risk of developing stroke or systemic embolism.

ADDENDUM – July 2012

Product: Dabigatran etexilate, capsules, 110 mg and 150 mg (as mesilate), Pradaxa[®]

Sponsor: Boehringer Ingelheim Pty Limited

Date of PBAC Consideration: July 2012

Purpose of Application:

The submission sought to address the matters raised by the PBAC in its advice to the Minister in March 2011 in recommending an extension to the Authority Required listing to include the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (NVAF) who are at moderate to high risk of developing stroke or systemic embolism, who meet certain criteria because based on the advice of the PBAC the Government is undertaking a *Review of Anticoagulation Therapies in Atrial Fibrillation*.

Background:

On 30 September 2011, the Government announced that it would commission Emeritus Professor Lloyd Sansom AO to inform the Government on options for improving the health outcomes of patients treated with anticoagulation therapies, including optimising the use of currently available treatments in Australia as well as the future role of newer therapies for the treatment of atrial fibrillation, such as dabigatran (Pradaxa[®]).

<http://pbs.gov.au/info/publication/factsheets/shared/anticoagulation-review>

Summary of Submission and Findings:

The submission presented additional sensitivity analyses in the modelled economic evaluation regarding the efficacy of dabigatran versus optimal warfarin therapy.

Time in Therapeutic Range (TTR) as a Measure of Warfarin Control

The submission presented some discussions around the use of time in therapeutic range (TTR) as a measure of warfarin control.

Optimal Warfarin Control

The submission presented an additional reference (Connolly et al (2008)) which considered the benefits of dose adjusted warfarin versus clopidogrel plus aspirin. The submission also presented the results of a *post-hoc* analysis of the outcomes of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W) trial, stratifying patients by their mean centre TTRs (cTTR) categories.

The Quality of Warfarin Control in Australia

In addition to the evidence previously presented at the March 2011 PBAC meeting, this submission presented two abstract publications reporting estimates of warfarin TTR in Australian Clinical practice.

TTR in RE-LY

The submission argued that if an analysis by TTR were to be undertaken, a more appropriate stratification would be by centre TTR (cTTR) as this would preserve the randomisation within each centre.

Literature Review of the Relationship Between TTR and Health Outcomes

The submission presented additional references, Rose et al (2011), White et al (2007), Jones et al (2005), Morgan (2009) and Connolly et al (2008) to discuss the relationship between warfarin TTR and health outcomes.

Economic Analysis

The submission presented the same model from the March 2011 submission, but included additional components to simulate optimal warfarin treatments for a sensitivity analysis.

Three modelling approaches were used in the sensitivity analysis:

1. Using the estimates of subgroups formed from the *a priori* defined centre time in therapeutic range (cTTR) cut-offs of the RE-LY trial to populate model efficacy estimates. The warfarin arm of the model was divided into subgroups groups of either cTTR <60% and ≥60% or cTTR <65% and ≥65%;
2. Using published estimates (from Jones et al (2005)) to adjust the efficacy of warfarin for a given level of TTR, and
3. Only considering dabigatran's benefits with respect to intracranial haemorrhage.

The table below summarises of the main differences and similarities between the model used in the sensitivity analysis and the one considered at the March 2011 PBAC meeting.

Model	March 2011 submission	July 2012 submission
Comparator	Base case: 50/50 each dose of dabigatran versus 50/50 warfarin aspirin	Similar base case, but additional sensitivity analysis.
Population	Economic model is based on the population of RE-LY trial.	No changes were made to modelled population. Therefore differences between the TTR subgroups reflect only efficacy differences and not underlying population differences.
Time horizon	Life time was presented. The PBAC noted a preference for 20 years.	Results reported over a lifetime and over 20 years.
Structure	Based on the model by Sorensen et al (2009).	<p>Model structure is largely unchanged from March 2011, but includes an optimal adjusted warfarin arm, where event rates reflect different assumptions about the effectiveness of “optimal” warfarin relative to warfarin use in RE-LY trial.</p> <p>The warfarin arm of the model is populated by subgroups in RE-LY that were enrolled with trial centres that reported total mean time in therapeutic range (cTTR). The pre-specified cTTR cut offs for the clinical trial report were used to define the patient subgroups (60% and 65%). Thus the sensitivity analyses considered warfarin patients in subgroups of either cTTR <60% and ≥60% or cTTR <65% and ≥65%.</p> <p>This grouping differs to what the PBAC considered at the March 2011 meeting, where the study report by Wallentin et al (2010) had classified RE-LY patients into quartiles by cTTR of: cTTR <57.1%, 57.1-65.5%, 65.5-72.6% and >72.6%.</p>

Recommendation and Reasons:

The submission sought to address the matters raised by the PBAC in its advice to the Minister in March 2011 because based on the advice of the PBAC the Government is undertaking a *Review of Anticoagulation Therapies in Atrial Fibrillation*.

In March 2011, the PBAC recommended the PBS listing of dabigatran 150 mg and an extension to the listing of dabigatran 110 mg for the prevention of stroke or systemic embolism in high-risk patients with non-valvular atrial fibrillation on the basis of acceptable cost effectiveness. In addition, the PBAC advised the Minister of the following:

- Dabigatran represents a safe, efficacious and cost effective therapy for ‘at risk’ patients with atrial fibrillation for the reduction of stroke and systemic thromboembolism. These reductions represent important reductions in morbidity, and can be expected to result in mortality reductions.
- Based on the high incidence of atrial fibrillation (which increases with increasing age) and the financial estimates in the submission over the first four years of listing, the Committee noted that the opportunity cost to the Commonwealth of listing dabigatran would be significant. The PBAC noted that dabigatran derives its advantage over warfarin when warfarin is used suboptimally and also noted that improving the use of

warfarin, by means of an education campaign aimed at prescribers, pharmacists and patients would be less costly.

- A number of patients who are currently reluctant to take warfarin because of the stringent monitoring requirements and interactions with other drugs and foods, but who should be taking oral anticoagulation based on available evidence, would now be treated with dabigatran and this would likely lead to additional benefits and costs not measured in the trial.
- The listing of dabigatran may result in patients at low risk currently managed on aspirin being unnecessarily transferred to dabigatran at a much higher cost, although the submission proposed a risk share arrangement to address this possibility.
- Medicare Australia would not be able to enforce compliance with the risk factors under a 'streamlined' authority, but would need to increase its workforce to deal with the number of telephone requests, if listed as 'Authority Required'.
- The PBAC considered that a 'streamlined' authority listing would likely lead to use outside the intended population (to less severe patients) but notes the high cost of implementing an 'Authority required' listing to Medicare Australia and therefore considers such an option impractical.
- Although dabigatran was superior to warfarin in the RE-LY ITT population, this benefit may or may not be reflected wholly in the Australian population.
- The effectiveness of dabigatran in patients who are not fully compliant with the twice daily dosing regimen is unknown, but given its pharmacology it is likely to be reduced in poorly compliant patients.
- Overall, with better control of warfarin and less compliance with dabigatran, the modelled gain in benefit with dabigatran would be reduced.
- In the event of PBS listing, the National Prescribing Service should carry out an education campaign on the prescribing of oral anticoagulation therapy.
- Alternative similar treatments are expected to come to the market shortly. These include apixaban, rivaroxaban, edoxaban and darexaban.

The PBAC noted the revised price for this indication and the revised price for the other currently listed PBS indications as well as the proposal for a revised risk-sharing arrangement, but noted that the opportunity cost remains high.

The PBAC considered the arguments made by the submission on a number of aspects discussed in March 2011, including those in relation to time in therapeutic range (TTR) as a measure of warfarin control; optimal warfarin control; the quality of warfarin control in Australia; and TTR in the RE-LY trial. The PBAC also noted the additional studies used by the submission to support the similarity of RE-LY trial population and Australian patients, and for compliance with dabigatran. A revised modelled economic evaluation was also presented to incorporate *post-hoc* subgroup efficacy outcomes using the a priori defined cTTR cut-offs from the RE-LY trial.

After consideration of the evidence and analyses presented in the submission, the PBAC confirmed its previous recommendation and advice to the Minister.

The new sensitivity analyses conducted during the evaluation of the minor submission show that the cost-effectiveness ratio of dabigatran is sensitive to the proportion of aspirin vs warfarin used in clinical practice and the proportion of use of the 110mg dose for which there is no evidence of additional treatment benefit over warfarin to justify a higher price.

Finally, the PBAC noted that, since the PBAC recommendation, the TGA issued Safety Advisory Alerts for dabigatran on 5 October and 3 November 2011, noting bleeding-related adverse events reports and advising of renal function monitoring requirements.

Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

Sponsor's Comment

The sponsor has no comment.

ADDENDUM – MARCH 2013

STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION REVIEW

Product: Dabigatran etexilate, capsules, 110 mg and 150 mg, Pradaxa[®]

Sponsor: Boehringer Ingelheim Pty Ltd

Date of PBAC Consideration: March 2013

1. Purpose of Application

To assess revised multivariate sensitivity analyses provided by the three sponsors of the New Oral Anticoagulants (NOACs) (dabigatran etexilate (dabigatran), rivaroxaban and apixaban) in response to the PBAC's request of December 2012 for new analyses. The new analyses were requested following the completion of the Final Report of the Review of Anticoagulation Therapies in Atrial Fibrillation (the Review), new information concerning comparative safety and consideration of management of anticoagulation therapy, including warfarin as well as new agents, in Australian clinical practice.

2. Background

In December 2012, the PBAC considered a request from the Minister for Health to "reconsider its previous recommendation from March 2011 for dabigatran (Pradaxa) consistent with subsection 101(3) of the *National Health Act 1953*" in the light of the Final Report of the Review of Anticoagulation Therapies in Atrial Fibrillation (the Review), which was also provided to the PBAC.

The PBAC noted the findings of the Review, which presented an updated consideration of all NOACs trials (dabigatran, rivaroxaban and apixaban) and an assessment of new information concerning comparative safety as well as consideration of management of warfarin therapy in the Australian context.

The Review's conclusion was that "the data from the trials indicate that generally, the NOACs are at least non-inferior to warfarin in regard to the primary outcomes of stroke/systemic embolism and major bleeding and are superior to warfarin with respect to the rate of intracranial bleeding and haemorrhagic stroke (HS)." The PBAC also noted the

comparison of the numbers needed to treat (NNTs) for the various outcomes as presented in the review and agreed that these estimates suggest large numbers of patients need to be treated with the NOACs to obtain small benefits at population level.

The PBAC noted the consideration in the Review with respect to intracranial haemorrhage (ICH) and agreed that the most consistent finding across all trials of NOACs was the beneficial effect on this outcome. The PBAC noted and endorsed the comments in the Review about the importance of this outcome to patients and clinicians. The PBAC also noted that the primary outcomes in the trials were influenced to a large extent by the estimates of frequency of ICH. However, the absolute numbers of these events in the trials were noted to be small and thus likely to be an imprecise estimate of benefit in real clinical practice.

The PBAC was concerned about the combined effect of the following inputs on the base-case cost-effectiveness ratio previously calculated for dabigatran in March 2011 and more recently, in 2012, for the other two drugs:

- type of clinical event for which an advantage should be modelled – the consensus was that only intracranial bleeding and haemorrhagic stroke (as the most consistent benefit seen in all NOAC trials), should be valued in this regard.
- proportion of NOAC (dabigatran, rivaroxaban, apixaban) replacing warfarin and aspirin – analyses should be heavily weighted towards warfarin as the therapy being replaced, (modelling should examine 80-100% warfarin rather than 50:50).
- PBAC noted more use in elderly patients (> 75 years) than initially assumed and given the increased risk of bleeds in the elderly population this also needs to be examined in modelling
- shorter time horizon of the model – given the older age of patients in clinical practice compared to the trials, PBAC felt that time horizons between 10 and 20 years should be modelled.
- In addition for dabigatran, the split between 110mg and 150mg dosing – PBAC noted more use of the 110mg dose in clinical practice than initially assumed and this should be reflected in modelling

The PBAC requested that multivariate analyses be provided by all three sponsors, using the revised parameters outlined above (together with costs offsets in relation to monitoring international normalised ratio (INR) added to the cost of warfarin). Sensitivity analyses should include incremental cost-effectiveness ratios (ICERs) based on the 95% confidence intervals of clinical event rates as well as point estimate, to further assist the PBAC in forming a view as to whether the newly estimated ICERs are in an acceptable range.

With respect to dabigatran, the PBAC also indicated that pending the outcomes of the further modelling outlined above, the PBAC was of a mind to rescind its original March 2011 recommendation, on the grounds that based on the new information, the cost effectiveness as originally estimated in the submission was not likely to be reflected in current clinical practice.

Finally, while noting the comparisons provided in the Review, the PBAC considered that it did not have sufficient evidence available to it at that time to determine whether there were clinically important differences between the three NOACs that should be taken into account.

3. PBAC consideration of the evidence

All sponsors provided submissions, which were evaluated. The submissions included revised sensitivity analyses, revised prices and risk-sharing arrangements

The PBAC noted the most recent safety analyses for dabigatran conducted by the Food and Drug Administration (FDA) (released in November 2012), by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use, as well as by the Therapeutic Goods Administration (TGA). The TGA has updated the Australian approved Product Information to reflect the latest safety data.

The PBAC also noted the publication of the extended follow up of patients from dabigatran's RE-LY trial - the RELY-ABLE trial, which provided an additional 2.3 years of follow-up dabigatran data (Connolly et al., 2012).

The PBAC further noted that the sponsor of dabigatran also stated that ischaemic strokes are the most common types of strokes and the prevention of these events is one of the primary aims of anticoagulation treatment in patients with atrial fibrillation.

Overall, the PBAC re-affirmed its view that all three NOACs are superior to warfarin with respect to the rate of intracranial bleeding and haemorrhagic stroke, and this is the most consistent benefit seen in the NOACs trials. An economic analysis focused on valuing these two types of events is the most conservative estimate of cost-effectiveness.

In addition, based on all the evidence it has considered to date about the three NOACs, including the Review, the PBAC considered that there are no clinically significant differences between the three NOACs that should be taken into account.

4. Economic Analysis

The PBAC noted the challenges of making comparisons across the multivariate sensitivity analyses of the three submissions, given that each submission adopted a distinct economic modelling approach.

The PBAC considered that comparative summary tables prepared during the evaluation demonstrated that the incremental cost-effectiveness ratios vary across models, and with events, and that modelling approaches were driving the differences in estimated ICERs.

It was for this reason that, during the evaluation, an attempt was made to standardise the modelling approach in terms of structure and inputs, using different multivariate analyses in what was referred to as the "revised base-case" by the evaluators. The multivariate scenarios started with the most conservative approach in which only HS was included, substitution is only from warfarin and the time horizon of the analysis is 15 years. The incremental cost-effectiveness ratio for dabigatran was between \$45,000 and \$75,000 per QALY gained.

Other parameters were varied to test the impact of various assumptions on the results. For example, when the ICH events were added (and HS, the 15 year time horizon and 100% warfarin substitution rate retained) the incremental cost-effectiveness ratio for dabigatran was between \$15,000 and \$45,000 per QALY gained.

The PBAC agreed that there will be substitution of patients not only from warfarin, but also from aspirin and potentially from no current treatment as observed in clinical practice in New Zealand. Such substitution patterns will lower the incremental cost-effectiveness ratios further.

5. Recommendation and Reasons

Since the March 2011 advice to the Minister recommending the PBS listing of dabigatran, the following new information has emerged:

- The Final Report of the Review of Anticoagulation Therapies in Atrial Fibrillation
- The RELY-ABLE data
- New experience of use of dabigatran in clinical practice which had accumulated beyond what was originally presented in the trials, including new safety analyses conducted by regulatory agencies
- New multivariate sensitivity analyses presented in the dabigatran minor submission
- New multivariate sensitivity analyses conducted during the evaluation of the dabigatran minor submission
- The availability for the consideration of the PBAC at its March 2013 meeting of an alternative therapy with a lower incremental cost-effectiveness ratio versus warfarin, namely rivaroxaban.

As a consequence, the PBAC made a new recommendation for dabigatran which varies its initial recommendation of March 2011 as follows:

The PBAC recommended the listing of dabigatran on the PBS on a cost-minimisation basis to rivaroxaban for the prevention of stroke in patients with non-valvular atrial fibrillation, with the equi-effective dose based on average doses in the trials, and subject to the same risk-sharing arrangement and PBS restriction.

The PBAC recommended the PBS listing of rivaroxaban for the prevention of stroke in patients with non-valvular atrial fibrillation at the price proposed in the minor submission on a cost-effectiveness basis in comparison with warfarin for the two outcomes, intracranial bleeding and haemorrhagic stroke, identified by the Review as being of most significance.

The PBAC advised that a risk-sharing arrangement, which would include a financial cap with a 100% rebate, would be an appropriate way of managing the total cost of this therapeutic area to the PBS.

Recommendation:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
DABIGATRAN			Pradaxa	BY
Dabigatran etexilate 110 mg capsule, 60	1	5		
Dabigatran etexilate 150 mg capsule, 60	1	5		

Condition/Indication:	Prevention of stroke or systemic embolism
Restriction:	Authority required (STREAMLINED)

Clinical criteria:	Patient must have non-valvular atrial fibrillation AND Patient must have one or more risk factors for developing stroke or systemic embolism.
Prescriber Instructions	Risk factors for developing stroke or systemic ischaemic embolism are: <ul style="list-style-type: none"> i. Prior stroke (ischaemic or unknown type), transient ischaemic attack or non-central nervous system (CNS) systemic embolism; ii. age ≥ 75 years; iii. hypertension; iv. diabetes mellitus; v. heart failure and/or left ventricular ejection fraction $\leq 35\%$.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.

6. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

7. Sponsor's Comment

Boehringer Ingelheim has been trying to make dabigatran available to Australian patients with non-valvular atrial fibrillation since the positive recommendation in March 2011 and will continue to make every effort to facilitate PBS listing.