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 ≥ 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

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).	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. 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%. 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%.

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.