**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<br>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<br>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<br>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<br>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<br>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<br>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.