**PUBLIC SUMMARY DOCUMENT**
**Product:** RIVAROXABAN, tablet, 15 mg and 20 mg, Xarelto®
**Sponsor:** Bayer Australia Ltd
**Date of PBAC Consideration:** March 2012

## 1. Purpose of Application

The submission sought an Authority Required (STREAMLINED) listing for the prevention of stroke and systemic embolism in a patient with non-valvular atrial fibrillation (NVAF), who is at risk of developing stroke or systemic embolism as evidenced by prior stroke (ischaemic or unknown type), transient ischaemic attack (TIA) or non-CNS systemic embolism or two or more of the following risk factors:

i. age ≥ 75 years;
ii. hypertension;
iii. diabetes mellitus;
iv. heart failure and/or left ventricular ejection fraction ≤ 35%

A separate submission requesting an Authority Required (STREAMLINED) listing for rivaroxaban for the initial and continuing treatment of confirmed acute symptomatic deep vein thrombosis (DVT) without symptomatic pulmonary embolism (PE), and for the prevention of recurrent venous thromboembolism (VTE) was also considered at the March 2012 PBAC meeting.

## 2. Background

Rivaroxaban had not been previously considered by the PBAC for this indication.

At its March 2009 meeting, the PBAC recommended an Authority Required listing of rivaroxaban tablet 10 mg for the prevention of venous thromboembolism in adult patients undergoing elective total replacement of the hip or knee on the basis of uncertain but overall acceptable cost-effectiveness compared with enoxaparin.

## 3. Registration Status

Rivaroxaban 15 mg and 20 mg tablets were TGA registered on 13 April 2012 for the following indications:

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke;
- Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE).

## 4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)

Prevention of stroke or systemic embolism in a patient with non-valvular atrial fibrillation (NVAF) who is at risk of developing stroke or systemic embolism as evidenced by prior stroke (ischaemic or unknown type), TIA or non-CNS systemic embolism or two or more of the following risk factors:

i. age ≥ 75 years;
ii. hypertension;

iii. diabetes mellitus;
iv. heart failure and/or left ventricular ejection fraction ≤ 35%.

*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. AF is triggered by atrial premature depolarisations arising in the region of the pulmonary veins and propagates in an irregular and unsynchronised pattern, producing irregularity in the pattern of ventricular activation. The disturbed atrial and ventricular activation creates a hypercoagulable state due to haemostasis in the left atrium which leads to thrombus formation, increasing the risk of stoke and other thrombolic events.

The submission proposed that the place in therapy of rivaroxaban is comparable to dabigatran as a treatment alternative to warfarin for stroke prevention in atrial fibrillation.

## 6. Comparator

The submission nominated dabigatran as the main comparator. The PBAC agreed that this was appropriate. The PBAC also noted the secondary comparison with warfarin.

## 7. Clinical Trials

The submission presented:

- one direct randomised trial comparing 20 mg and 15 mg rivaroxaban (15 mg rivaroxaban was used in patients with moderate renal impairment (CrCL = 30 to 49 mL/min) and was not a separate treatment arm in the trial) with dose-adjusted warfarin (ROCKET), and
- one direct randomised comparative trial comparing 150 mg and 110 mg dabigatran (separate treatment arms in the trial) with dose-adjusted warfarin (RE-LY).

Details of the trials published at the time of the submission are in the table below.

**Trials and associated reports presented in the submission**

| Trial | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **Direct randomised trials** | | |
| **Rivaroxaban versus warfarin** | | |
| ROCKET<br>Aalbers J | Rivaroxaban equals warfarin treatment in atrial fibrillation patients at high risk of stroke. | Cardiovascular Journal of Africa. 2011; 21(6): 342-343. |
| Patel MR, et al. | Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. | New England Journal of Medicine. 2011; 365(10):883-91. |
| **Indirect comparison: warfarin as common reference** | | |
| **Dabigatran versus warfarin** | | |
| RE-LY<br>Aulin JK, et al. | Interleukin-6 and C-reactive protein and risk for death and cardiovascular events in patients with atrial fibrillation. | J Am Coll Cardiol. 2011; 57(14 S1): E91. |
| Connolly SJ, et al | Dabigatran versus warfarin in patients with atrial fibrillation. | N Engl J Med 2009; 361:1139-1151. |

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|---|---|---|
| Diener HC, et al | Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. | Lancet Neurol 2010; 9:1157–1163. |
| Diener HC, et al | Reduced Cerebral Bleeding Rates with Dabigatran Compared to Warfarin in Patients with Atrial Fibrillation: Results of RE-LY. | American Academy of Neurology 62nd Annual Meeting 2010. |
| Diener HC. | Dabigatran compared to warfarin in patients with atrial fibrillation and prior TIA or stroke: results of RE-LY. | Int J Stroke 2010; 5(S2): 40. |
| Eikelboom JW, et al | Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: An analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) Trial. | Circulation. 2011; 123:2363-2372. |
| Ezekowitz MD, et al | Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. | Circulation. 2010; 122:2246-2253. |
| Healey JS, et al | Effect of age and renal function on the risks of stroke and major bleeding with dabigatran compared to warfarin: An analysis from the RE-LY study. | J Am Coll Cardiol. 2010; 55 (10 S1): A4.E37. |
| Hijazi Z, et al | Troponin I elevation increases the risk of death and stroke in patients with atrial fibrillation. | Eur Heart J 2010; 31(S1): 886. |
| Hori M, et al. | Efficacy and Safety of Dabigatran vs. Warfarin in Patients With Atrial Fibrillation - Sub-Analysis in Japanese Population in RE-LY Trial. | Circ J. 2011; 75: 800-805. |
| Koti MJ, et al | Dabigatran versus warfarin in patients with atrial fibrillation - An analysis of patients undergoing cardioversion. | J Am Coll Cardiol. 2010; 55 (10 S1): A4.E40. |
| Nagarakanti R, et al | Dabigatran versus warfarin in patients with atrial fibrillation: An analysis of patients undergoing cardioversion. | Circulation. 2011; 123: 131-136. |
| Oldgren J, et al. | Dabigatran Versus Warfarin In Atrial Fibrillation Patients With Low, Moderate And High Chads2 Score: A RE-LY Subgroup Analysis. | J Am Coll Cardiol. 2010; 55 (10 S1): A1.E2. |
| Paikin JS, et al | Dabigatran for stroke prevention in atrial fibrillation: the RE-LY trial. Expert Rev. | Cardiovasc. Ther. 2011; 9(3): 279–286. |
| 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; 376: 975–983. |
| Wallentin L, et al | Efficacy and safety of dabigatran compared to warfarin at different levels of INR control for stroke prevention in 18,113 patients with atrial fibrillation in the rely trial. | Circulation 2010; 120(21): 2158. |

The ROCKET and RE-LY trials were both non-inferiority trials versus dose-adjusted warfarin, with a pre-specified non-inferiority margin for the lower bound of the 95% CI of the risk (hazard) ratio of 1.46 for the primary outcome of stroke/systemic embolism (SE).

Based on ROCKET and RE-LY, the submission presented an indirect comparison between rivaroxaban and dabigatran, using warfarin as the common comparator. Both trials enrolled patients with non-valvular AF (NVAF). However, the PBAC noted that the ROCKET trial enrolled patients who were at higher risk ($CHADS_2 \geq 2$) compared to those enrolled in RE-LY ($CHADS_2 \geq 1$).

## 8. Results of Trials

### ROCKET – RIVAROXABAN VERSUS WARFARIN

The table below summarises the results of the composite primary outcome of stroke and non-CNS embolism from the ROCKET trial.

**Results of the primary efficacy endpoint in ROCKET - composite stroke and non-CNS embolism and results for the individual components (where reported) of the composite outcome (excluding site 042012[a])**

| Analysis method | Rivaroxaban n/N (%) [event rate^] | Warfarin n/N (%) [event rate^] | Rivaroxaban versus warfarin | | | | |
|---|---|---|---|---|---|---|---|
| | | | HR (95%CI) | p-value | | RD % (95% CI) | NNT (95% CI) |
| | | | | I | S | | |
| **Per protocol population** | | | | | | | |
| On treatment* Composite | 188/6958 (2.7) [1.71] | 241/7004 (3.44) [2.16] | **0.79 (0.66,0.96)** | **<0.001** | **0.018** | **-0.7 (-1.3, -0.2)** | **143 (77, 500)** |
| On treatment (restrictive definition)[#] | 186/6958 (2.67) [1.70] | 239/7004 (3.41) [2.14] | **0.79 (0.65,0.96)** | **<0.001** | **0.017** | **-0.7 (-1.3, -0. 2)** | **143 (77, 500)** |
| Last dose plus 30 days | 247/6958 (3.55) [2.16] | 279/7004 (3.98) [2.39] | 0.90 (0.76,1.07) | **<0.001** | 0.23 | -0.4 (-1.1, 0.2) | N/A |
| **Safety population** | | | | | | | |
| On treatment* | | | | | | | |
| Composite | 189/7061 (2.68) [1.70] | 243/7082 (3.43) [2.15] | **0.79 (0.65,0.95)** | **<0.001** | **0.015** | **-0.8 (-1.3, -0.2)** | **125 (77, 500)** |
| Stroke | 184/7061 (2.61) [2.61] | 221/7082 (3.12) [3.12] | 0.85 (0.75, 1.03) | NR | NR | -0.5 (-1.1, 0.4) | N/A |
| Non CNS SE | 5/7061 (0.07) [0.07] | 22/7082 (0.31) [0.31] | 0.23 (0.09, 0.61) | NR | NR | **-0.24 (-0.41, -0.1)** | 417 (243, 1,000) |
| **ITT population** | | | | | | | |
| Follow-up visit[$] | 257/7081 (3.80) [2.18] | 285/7090 (0.40) [2.39] | 0.91 (0.77,1.08) | **<0.001** | 0.286 | -0.04 (-1.02, 0.24) | N/A |
| Site notification[&] | | | | | | | |
| Composite | 269/7081 (3.80) [2.12] | 306/7090 (4.32) [2.42] | 0.88 (0.74,1.03) | **<0.001** | 0.117 | -0.52 (-1.17, 0.13) | N/A |
| Stroke | 253/7081 (3.57) [3.57] | 281/7090 (3.96) [3.96] | 0.90 (0.76, 1.07) | **NR** | NR | -0.39 (-1.02, 0.24) | N/A |
| Non CNS SE | 20/7081 (0.28) [0.20] | 27/7090 (0.38) [0.38] | 0.74 (0.42, 1.32) | NR | NR | -0.10 (-0.30, 0.09) | N/A |
| Regardless of treatment exposure | | | | | | | |
| Composite | 293/7081 (4.14) [2.20] | 320/7090 (4.51) [2.40] | 0.91 (0.78,1.07) | **<0.001** | 0.263 | -0.38 (-1.05, 0.03) | N/A |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Stroke | 277/7081 (3.91) [2.07] | 295/7090 (4.16) [4.16] | 0.94 (0.80,1.10) | NR | 0.443 | -0.25 (-0.90, 0.40) | N/A |
| Non CNS SE | 20/7081 (0.28) [0.28] | 27/7090 (0.38) [0.38] | 0.74 (0.42,1.32) | NR | 0.309 | -0.10 (-0.3, 0.09) | N/A |

[a] Data from the Czech Republic (site 042012: 50 patients randomised to rivaroxaban, 43 patients randomised to warfarin) were deemed unreliable and excluded from the analysis due to evidence that source documents had been modified so that subjects appeared to meet the inclusion/exclusion criteria for enrolment. Also, five subjects were randomised twice; only data associated with the first randomisations were used for the ITT analyses.

^ Event Rate per 100 patient years: number of events per 100 patient years of follow up.

* On treatment is the period between the date of the first double-blind study medication to the date of the last double-blind study medication administration plus 2 days.

# On treatment (restrictive definition): if the subject has a temporary stop of the study medication before the efficacy endpoint event and re-starts the study medication after the efficacy endpoint event, the event is considered to occur while on treatment only if additionally its date is definitively within 2 calendar days from that temporary stop of the study medication.

$ ITT follow-up visit includes data from the 'post treatment follow-up visit' for early discontinuers and the 'end of study follow-up visit' for study completers

& Site notification is the notification to the site that the required primary efficacy endpoint events have been reached.

I p-value (one-sided) for non-inferiority of rivaroxaban versus warfarin by a non-inferiority margin of 1.46 in hazard ratio.

S p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio, upper limit was required to be <1.00.

The PBAC noted that the results for the comparison of rivaroxaban and warfarin showed that the non-inferiority margin of 1.46 was met, irrespective of the population (per protocol (PP), safety, and intention to treat (ITT)) used. For the claim of superiority of rivaroxaban over warfarin, the analyses based on the PP and safety populations showed statistically significant reductions in stroke/non-CNS events for patients treated with rivaroxaban compared with those treated with warfarin, but these reductions were not statistically significant when the analysis was based on the ITT population.

The submission stated that the "safety, on treatment" population, defined as those followed up while on treatment plus 48 hours following cessation of randomised therapy, was selected as the primary population for analysis because anticoagulants would not be expected to have a durable effect beyond the period of their pharmacodynamic activity, i.e., the "on treatment" period.

The submission presented results comparing the effectiveness of rivaroxaban with warfarin, according to time in therapeutic range (TTR; INR 2-3) stratified by study centre. The results of these analyses showed that the difference in TTR between study centres made little difference to the HR for the primary efficacy outcome. The test for interaction between the HR and TTR was non-significant. This was in contrast to the results from the RE-LY trial for dabigatran, where the treatment effect compared to warfarin was dependent on centre TTR. An analysis comparing rivaroxaban and warfarin according to median TTR was conducted during the evaluation. The results of this analysis indicated that:

- when the TTR was below the median, rivaroxaban was statistically significantly better than warfarin for the primary end point;
- when the TTR was above the median, there was no difference in the primary end point;
- when the TTR was above the median, the non-inferiority criterion of 1.46 was not met.

*For PBAC's view see Recommendation and Reasons*

**INDIRECT COMPARISON - RIVAROXABAN VERSUS DABIGATRAN**

The submission presented an indirect comparison of rivaroxaban versus dabigatran for the primary outcome of stroke/SE using various populations from the ROCKET trial (rivaroxaban versus warfarin) and the ITT population from RE-LY (dabigatran 150 mg and 110 mg versus warfarin), as well as indirect comparisons of the sub-group of patients in the RE-LY trial with a $CHADS_2$ score of 2 and of 3 or greater. These analyses are relevant because the population enrolled in the ROCKET trial were at higher risk of stroke (mean $CHADS_2$ score was 3.47) compared to those enrolled in RE-LY (mean $CHADS_2$ score was 2.1).

For the primary outcome of stroke/systemic embolism, indirect comparisons of rivaroxaban versus dabigatran showed that there were no statistically significant differences between rivaroxaban and either dose of dabigatran when the "safety, on treatment" population of the ROCKET trial were considered. The non-inferiority margin of 1.46 was met when the analyses used any of the PP, "safety, on treatment" and ITT rivaroxaban populations, compared to the dabigatran 110 mg ITT population. However, the non-inferiority margin of 1.46 was not satisfied for any of the rivaroxaban trial populations compared to the dabigatran 150 mg ITT population.

*For PBAC's view, see Recommendation and Reasons*

In ROCKET, the rates of major and non-major clinically relevant bleeding were similar in the rivaroxaban and warfarin groups (p=0.422). Fewer patients receiving warfarin experienced bleeding events leading to a drop in haemoglobin or requiring transfusion. In contrast, fatal or critical organ bleeding occurred less frequently in the rivaroxaban group, mainly because of lower rates of haemorrhagic stroke and other intracranial bleeding. The submission stated important findings were the lower incidences of intracranial haemorrhage (p=0.019), critical organ bleeds (0.82 versus 1.18 per 100 patient-years p=0.007), and bleeding related deaths (p=0.0003) with rivaroxaban compared with warfarin. More patients who received rivaroxaban had decreases in haemoglobin (p=0.019) or required transfusions (p=0.044). Major bleeding from a gastrointestinal site was more common with rivaroxaban compared with warfarin (p<0.001). Intracranial haemorrhage, including non-traumatic intraparenchymal and intraventricular haemorrhagic strokes, were more frequent in the warfarin treated group compared to the rivaroxaban group. The incidence of death in the rivaroxaban group was 5.19% and in the warfarin group it was 6.05%.

The overall incidence of treatment emergent adverse events (AEs) in ROCKET was similar in the rivaroxaban and warfarin groups. The types of events were also similar in both treatment groups although more patients in the rivaroxaban group had epistaxis compared with the warfarin group. However, very few cases in either treatment group were considered to be major bleeds (0.18% and 0.20% in the rivaroxaban and warfarin group, respectively); all cases in either treatment group were considered to be minimal bleeds. The numbers of treatment emergent serious AEs were similar between the rivaroxaban and warfarin groups. The numbers of patients who withdrew from treatment due to AEs were also similar in both treatment groups. The submission provided additional data on potential safety concerns beyond those identified in the clinical trials. The data presented did not report any new or unexpected information on efficacy or safety.

The submission presented an indirect comparison of rivaroxaban and dabigatran for several safety endpoints.

*For PBAC's view see Recommendation and Reasons*

## 9. Clinical Claim

The submission claimed that rivaroxaban is non-inferior to dabigatran in terms of efficacy and safety.

The submission claimed that rivaroxaban is more effective than warfarin at reducing stroke and systemic embolism and has better toxicity than warfarin demonstrated by a reduction in critical organ bleeds.

*For PBAC's view see Recommendation and Reasons*

## 10. Economic Analysis

Although nominated as the primary comparator, the submission stated that a cost-minimisation analysis against dabigatran was not possible given that the price is not publicly available. Therefore the submission presented two cost-utility analyses ('trial based' and 'modelled') against warfarin, based on the ROCKET trial.

**TRIAL-BASED ECONOMIC EVALUATION**

The submission presented a trial-based economic evaluation (Step 1) and the subsequent inclusion of costs associated with INR testing (Step 2), ongoing stroke costs (Step 3) and utilities (Step 4) over the duration of the trial period (18 months).

The incremental cost per QALY gained from the trial-based economic evaluation was between $15,000 and $45,000.

**MODELLED ECONOMIC EVALUATION**

A modelled economic evaluation was also presented. The time horizon of the model is 30 years, with 6-monthly cycles. Patients continue through the model until death or 60 cycles have been completed.

The base incremental cost per QALY gained from the modelled economic evaluation was between $15,000 and $45,000.

The PBAC considered that a 30-year time horizon may be excessive given the average age of patients in the ROCKET trial was approximately 70 years. In its consideration of the dabigatran submission, the PBAC considered that a time horizon of the model of 20 years was reasonable (March 2011, PSD). Patients enrolled in the RE-LY trial also had an average age of approximately 70 years. The ICER for rivaroxaban over 20 years was higher but remained within the range of $15,000 to $45,000/QALY.

The model was driven predominantly by differences in the event rates of haemorrhagic stroke (RR=0.59; 95% CI: 0.39, 0.89) and critical organ bleed (RR=0.69; 95% CI: 0.53, 0.89) in the rivaroxaban and warfarin arms, and subsequent death from these events, the risk of which was assumed to be different in the treatment arms (55% versus 64% for haemorrhagic stroke and 20% versus 31% for critical organ bleed for rivaroxaban and warfarin, respectively).

*For PBAC's view see Recommendation and Reasons*

## 11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated in the submission to be more than $100 million in Year 5 when only patients with a $CHADS_2$ score of ≥2 are considered or higher when patients with a $CHADS_2$ score of ≥1 are considered.

*For PBAC's view see Recommendation and Reasons*

## 12. Recommendation and Reasons

The PBAC noted that evaluation by the TGA was still in process and the final indication will inform the appropriateness of the requested restriction. The PBAC further noted that the requested restriction is narrower than that recommended by PBAC for dabigatran, as it requires eligible patients to have had prior stroke/TIA/systemic embolism or two or more of the listed risk factors. This equates to patients with a CHADS2 score of at least 2, consistent with the trial population in the ROCKET study. The PBAC considered that it would be difficult to enforce a CHADS score cut-point and that there was no clinical reason not to align the restriction for rivaroxaban to other anticoagulant therapy in atrial fibrillation.

The PBAC agreed that dabigatran was the appropriate comparator. The PBAC also noted the secondary comparison with warfarin.

For the primary outcome of stroke/systemic embolism, the PBAC noted that indirect comparisons of rivaroxaban versus dabigatran, using the ROCKET and RE-LY trials, indicated that the non-inferiority margin of 1.46 was met for analyses of the per protocol (PP), "safety, on treatment" and intention-to-treat (ITT) rivaroxaban populations when compared to the dabigatran 110 mg ITT population. However, the non-inferiority margin of 1.46 was not satisfied when any definition of the rivaroxaban trial population was compared to the dabigatran 150 mg ITT population. The PBAC considered that the relative safety of rivaroxaban versus dabigatran was uncertain because indirect comparisons between these agents are limited by the different definitions for bleeding in the ROCKET and RE-LY trials.

The PBAC considered that the submission's claim of rivaroxaban having non-inferior safety to warfarin was reasonable. However, the PBAC considered that based on the supporting data, the claim of superiority of rivaroxaban versus warfarin in reducing stroke and systemic embolism was uncertain. The population specified as being the primary analysis set was the "safety, on treatment" population, rather than the ITT population, who were followed up while on treatment and for 48 hours post randomised treatment cessation. As such, the PBAC considered that the outcomes for this population may not include relevant stroke and systemic embolism events which may have occurred over a longer period of follow-up. Analyses of the PP and "safety, on treatment" populations indicate a statistically significant reduction in stroke/non-CNS events for rivaroxaban compared to warfarin, but no statistically significant difference was observed for this outcome when the analysis was based on the ITT population. The PBAC considered that the applicability of the results of the ROCKET trial may be dependent on the compliance of patients who are prescribed warfarin, noting that rivaroxaban was only statistically significantly better than warfarin for the primary end point when the time to response (TTR) was below the median. The PBAC has previously noted that TTR varies between 50.4% and 68% in Australia (Public Summary Document for dabigatran, March 2011).

The PBAC noted that the submission presented two cost-utility analyses comparing rivaroxaban to warfarin, including:

- a 'trial-based' analysis giving a cost per QALY gained over a lifetime from the avoidance of events during the 18 month trial period (which produced and ICER of between $15,000 and $45,000 per QALY); and
- a 'modelled' analysis giving a cost per QALY gained over a time horizon of 30 years in the base case (which produced an ICER of between $15,000 and $45,000).

The PBAC agreed with the main areas of economic uncertainty as identified by the Economics Subcommitte for these economic evaluations. The PBAC considered that the clinical uncertainties associated with the claim that rivaroxaban is superior to warfarin resulted in uncertainty in the appropriateness of basing the economic evaluation on a cost-utility analysis. The PBAC noted that the "safety, on treatment" population was used to inform the 'modelled analysis', and as such, the economic evaluation may not capture important clinical events due to the premature cessation of follow-up in this population. The PBAC also noted that when no differences in any of the events are assumed, with the exception of a statistically significant difference in haemorrhagic stroke in the ITT population, the ICER becomes unacceptably high (between $45,000 and $55,000 per QALY).

The PBAC considered that the 'trial-based' analysis was not appropriate because the incremental cost in the ICER was the cost accumulated over the 18-month trial period but the QALYs were gained over a lifetime. That is, this analysis relies on an unreasonable assumption that no further events occur over a lifetime after 18 months of treatment. The PBAC also considered that it was not appropriate to apply an average QALY lost per first ever stroke from Cadilhac (2009) to subsequent strokes as this would likely underestimate the disutility from further strokes. The PBAC considered that overall, there is high uncertainty associated with the economic evaluation and it is likely that the ICER is higher than the submission's estimates.

The PBAC considered that the submission's estimates of financial implications to the PBS were highly uncertain and were likely significant underestimates. There is a considerable risk of use outside the population described in the restriction to those at lower risk ($CHADS_2$ score of $\geq 1$).

The PBAC therefore rejected the submission because of the uncertainty around the clinical evidence to support the clinical claim and the resultant uncertainty in the economic analysis.

In making this recommendation, the PBAC noted the consumer comments on this item.

***Recommendation***:
**Reject**

## 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

Bayer Australia will continue to work with the Pharmaceutical Evaluation Branch and the PBAC to make rivaroxaban available for patients with non-valvular atrial fibrillation.