PUBLIC SUMMARY DOCUMENT

Product: Rivaroxaban, tablets, 15 mg and 20 mg, Xarelto®
Sponsor: Bayer Australia Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application

The resubmission sought a second-line Section 85 Authority Required (STREAMLINED) listing for the prevention of stroke and systemic embolism in a patient with non-valvular atrial fibrillation (NVAF) who is inadequately controlled on warfarin or not suitable for warfarin.

2. Background

Rivaroxaban was previously considered by the PBAC at the March 2009 meeting, where 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.

In the March 2012 meeting, the PBAC considered rivaroxaban for listing for the prevention of stroke and systemic embolism in patients with NVAF in March 2012. The PBAC recommended that the submission be rejected as it was considered that there was high uncertainty associated with the economic evaluation and it was likely that the ICER is higher than the submission's estimates.

See rivaroxaban's March 2012 Public Summary Document relating to stroke and systemic embolism for further information.

In March 2012, the PBAC also recommended extending rivaroxaban's PBS-listing to include the treatment of deep vein thrombosis.

3. Registration Status

Rivaroxaban is approved by the TGA for the following:

- Prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to five weeks; elective total knee replacement, treatment for up to two weeks);
- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke; and
- Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE).

The latter two indications were TGA registered from the 13 April 2012.

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%

Patients must be inadequately controlled on warfarin or not suitable for warfarin

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 stroke and other thrombolic events.

Rivaroxaban was proposed as an alternative to warfarin and aspirin.

6. Comparator

The submission nominated warfarin and aspirin as the main comparators. Given that the requested restriction was for patients inadequately controlled on warfarin or for whom warfarin is not suitable, the PBAC considered that aspirin was the more appropriate comparator. The PBAC noted, however, that aspirin is not the appropriate therapy for patients with a $CHADS_2$ score of greater than or equal to two (an estimation of the risk of stroke based on the presence of Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes and prior Stroke or transient ischaemic attack, with higher scores indicating an increased risk) and therefore the selection of the comparator might need to include consideration of different risk scores of different groups of patients. The PBAC considered that dabigatran may also be a relevant comparator.

7. Clinical Trials

The submission presented a post hoc subgroup analysis of patients who had a time in therapeutic range (TTR) with warfarin treatment below the median reported in the ROCKET trial against the entire rivaroxaban treatment arm in ROCKET. ROCKET is a randomised trial comparing rivaroxaban 20 mg per day (patients with moderate renal function received 15 mg per day) with dose-adjusted warfarin in patients with non-valvular atrial fibrillation with prior stroke or at least two risk factors for stroke (the equivalent of a $CHADS_2$ score of greater than or equal to two). The submission presented this subgroup analysis to represent the patient population in the requested restriction of patients who are not adequately controlled on warfarin. The PBAC noted that the subgroups were not defined by pre-randomisation characteristics.

The submission also presented a meta-analysis of ten randomised trials comparing aspirin (75-325 mg per day) with dose adjusted warfarin in patients with non-valvular atrial fibrillation (NVAF) (no additional requirement for stroke risk factors were reported). The submission then presented an indirect comparison of the ROCKET trial and the meta-analyses of the warfarin versus aspirin trials to inform the efficacy and safety of rivaroxaban versus aspirin.

The PBAC considered advice that the indirect comparison of rivaroxaban and aspirin should be interpreted cautiously as the comparability of the trials included in the analysis is questionable, given the stroke risk of patients enrolled, the years over which the trials were conducted and the potential that standard management of patients with AF may have changed over the period of time that the aspirin and ROCKET trials were conducted.

No efficacy or safety data for rivaroxaban was presented in the re-submission specifically for patients who are inadequately controlled or not suitable for warfarin. The approach taken by the re-submission was likely to have overestimated the relative efficacy of rivaroxaban versus warfarin, particularly if reasons for not achieving an above median TTR would also apply to rivaroxaban (such as compliance). Analyses conducted during the evaluation demonstrated that there was a difference between the patients in the warfarin arm of the trial who had below and above median TTR with respect to prior vitamin K antagonist (VKA) and aspirin use.

Details of the trials published at the time of submission are shown below.

Trial/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Rivaroxaban versus warfarin		
ROCKET Aalbers J et al.	Rivaroxaban equals warfarin treatment in atrial fibrillation patients at high risk of stroke.	*Cardiovascular Journal of Africa* (2011); 21(6): 342-343.
Alexander W et al.	American Heart Association 2010 Scientific Sessions and American Society of Nephrology: Renal Week 2010. 43rd Annual Meeting & Scientific Exposition. Preventing stroke with Rivaroxaban (Xarelto) - The ROCKET-AF trial	*P T* (2011); 36(1):46.
Patel MR et al.	Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.	*New England Journal of Medicine* (2011); 365(10):883-91.
Fox KA et al.	Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment	*European Heart Journal* (2011); 32(19):2387-94.
Hankey GJ et al.	Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF.	*Lancet Neurology* (2012);11(4):315-22.
Mahaffey KW et al.	Ischemic cardiac outcomes in patients with af treated with vitamin k antagonism or factor XA inhibition: Results from the rocket AF Trial	*Circulation* (2011); 124(21).
The Executive Steering Committee, on behalf of the ROCKET AF Study Investigators	Rivaroxaban-Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: Rationale and Design of the ROCKET AF study	*American Heart Journal* (2010); 159(3):340-7.
Indirect comparison: warfarin as common reference		
Warfarin versus 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	*The Lancet* (1989); 1(8631):175-9.

	Copenhagen AFASAK Study.	
AFASAK II Gulløv AL et al	Fixed Minidose 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 The AFASAK 2 Study	*Archives of Internal Medicine* (1999); 159:1322-1328
Koefoed BG et al.	.Effect of fixed minidose warfarin, conventional dose warfarin and aspirin on INR and prothrombin fragment 1 + 2 in patients with atrial fibrillation.	*Thrombosis & Haemostasis* (1997); 77(5):845-8.
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.	*The Lancet* (2007); 370: 493–503
EAFT	Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group.	*The Lancet* (1993); 342: 1255-62.
Hu D et al.	The randomized study of efficiency and safety of antithrombotic therapy in nonvalvular fibrillation: warfarin compared with aspirin.	*Chinese Journal of Cardiology* (2006); 34(4): 295-298
Lu Y et al	Anticoagulant treatment on chronic non-valvular atrial fibrillation in the elderly patients.	*Chinese Journal of Emergency Medicine* (2006); 15(1): 54-56
PATAF Hellemons BSP et al.	Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin.	*British Medical Journal* (1999); 319: 958-964.
SPAF II Stroke Prevention in Atrial Fibrillation Investigators	Stroke Prevention in Atrial Fibrillation Study. Final Results.	*Circulation* (1991); 84: 527-539.
Vemmos KN et al.	Primary prevention of arterial thromboembolism in the oldest old with atrial fibrillation – a randomized pilot trial comparing adjusted-dose and fixed low-dose coumadin with aspirin.	*European Journal of Internal Medicine* (2006); 17: 48-52.
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 of patient-relevant outcomes across the direct randomised trials and indirect comparisons are shown in the table below.

Analysis	OR (95% CI)	RR (95% CI)	RD (95% CI)	NNT (95% CI)
Ischaemic stroke				
ROCKET ITT	0.99 (0.82, 1.21)	0.99 (0.82, 1.20)	-0.02 (-0.06, 0.06)	NA
Meta-analysis	**2.22 (1.66, 2.98)**	**2.10 (1.60, 2.78)**	**2.9 (1.4, 4.3)**	34 (23, 71)
Indirect comparison[a]	**0.45 (0.31, 0.63)**	**0.47 (0.34, 0.66)**	**-2.9 (-4.4, -1.5)**	34 (23, 68)
Haemorrhagic Stroke				

ROCKET ITT	**0.58 (0.38, 0.89)**	**0.58 (0.38,0.89)**	**-0.3(-0.6,-0.1)**	333 (166, 1000)
Meta-analysis	0.77 (0.30, 1.97)	0.77 (0.30,1.96)	-0.1 (-0.6,0.4)	NA
Indirect comparison[a]	0.75 (0.27, 2.11)	0.75 (0.27, 2.11)	-0.2 (-0.8, 0.4)	NA
Non- CNS Embolism (Systemic embolism)				
ROCKET ITT	0.74 (0.42, 1.32)	0.74 (0.42,1.32)	-0.1 (-0.2,0.1)	NA
Meta-analysis	**1.84 (1.11,3.04)**	**1.77 (1.11, 2.85)**	0.3 (-0.5,1.1)	NA
Indirect comparison[a]	**0.40 (0.19, 0.86)**	**0.42 (0.20, 0.88)**	-0.4 (-1.2, 0.4)	NA
Haemoglobin Haematocrit Drop				
ROCKET ITT	**1.21 (1.02, 1.44)**	**1.20 (1.02, 1.42)**	**0.7 (0.1,1.4)**	142 (71, 1000)
Transfusion				
ROCKET ITT	1.24 (0.99,1.54)	1.23 (0.99, 1.52)	0.5 (-0.01, 1.0)	NA
Critical Organ bleeding				
ROCKET ITT	**0.68 (0.52, 0.89)**	**0.69 (0.53, 0.89)**	**-0.6 (-1.0,-0.2)**	167 (100, 500)
Intracranial Haemorrhage				
ROCKET ITT	**0.65 (0.46, 0.92)**	**0.66 (0.47, 0.92)**	**-0.4 (-0.7,-0.1)**	250 (143, 1000)
Meta-analysis	0.64 (0.34,1.20)	0.64 (0.34, 1.19)	--0.4 (-1.0,0.2)	NA
Indirect comparison[a]	1.32 (0.82, 2.14)	1.35 (0.64, 2.86)	0.2 (-0.4, 0.8)	NA
Major bleeding				
ROCKET ITT	1.03 (0.89, 1.19)	1.03 (0.89, 1.18)	0.1 (-0.6,0.9)	NA
Meta-analysis	0.60 (0.29, 1.24)	0.61 (0.31, 1.23)	-1.2 (-2.9, 0.5)	NA
Indirect comparison[a]	1.72 (0.82, 3.6)	1.69 (0.84, 3.41)	1.6 (-0.5, 3.7)	NA
Death (due to major bleeding)				
ROCKET ITT	**0.49 (0.31, 0.78)**	**0.49 (0.31, 0.78)**	**-0.4 (-0.6,-0.1)**	250 (167, 1000)
Minor (Minimal) Bleed				
ROCKET ITT	1.15 (0.96, 1.38)	1.14 (0.96, 1.36)	0.5 (-0.1,1.1)	NA
Meta-analysis	**0.46 (0.34, 0.61)**	**0.52 (0.38, 0.71)**	**-5.6 (-10.9, -0.2)**	18 (9, 500)
Indirect comparison[a]	**2.5 (1.77, 3.53)**	**2.19 (1.53, 3.14)**	**6.1 (0.72, 11.5)**	16 (9, 140)

Results for the below median TTR subgroup of the ROCKET trial are unpublished and so are not displayed.

[a] all indirect comparisons were conducted using the ROCKET (ITT) data and the results of the meta-analyses from the warfarin versus aspirin trials

For the outcomes of haemoglobin haematocrit drop, transfusion and critical organ bleeding, no data for the comparison of warfarin versus aspirin were available. Instead, the re-submission assumed these outcomes to be a 'major bleed' event, and assumed that there was no difference between rivaroxaban and aspirin for haemoglobin haematocrit drop, transfusion and critical organ bleeding as the indirect comparison for major bleeding showed no statistically significant difference (OR = 1.72, 95% CI (0.82, 3.6)). The event rates for no treatment were derived from Lip et al (2006), which reported a relative risk of 3.03 for ischaemic stroke and non-CNS events and a bleed risk of 0.45 in patients treated with placebo versus warfarin. These relative risks were applied to the event rates of the warfarin treatment group in ROCKET to estimate the event rates in the no treatment group.

In comparison with the intention-to-treat (ITT) analysis of the ROCKET trial, the only outcome that became statistically significantly different between the treatments is ischaemic stroke when comparing the rivaroxaban and below median TTR subgroup of the warfarin treatment arm.

The PBAC considered that the subgroup of below median TTR was not representative of the requested PBS population and that the results from the subgroup analysis which was based on post-hoc drug response were not valid.

9. Clinical Claim

The re-submission described rivaroxaban as superior in terms of comparative effectiveness and superior in terms of comparative safety over warfarin. The re-submission also described rivaroxaban as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over aspirin.

As warfarin was probably not a relevant comparator for the group targeted in the proposed restriction, the PBAC was not able to interpret the submission's claim of superior efficacy and safety of rivaroxaban over warfarin.

The PBAC considered that the claims that rivaroxaban is superior in terms of comparative effectiveness and equivalent in terms of comparative safety over aspirin, are not adequately supported by the data presented in the re-submission.

10. Economic Analysis

The submission presented a cost utility analysis based on the claim of superior efficacy and safety versus warfarin and superior efficacy and equivalent safety compared with aspirin. The model produced an ICER of less than $15,000 per QALY over 20 years based on several outcomes (ischaemic and haemorrhagic stroke, non-CNS embolism, haemoglobin/haematocrit drop, transfusion, critical organ bleeds, major bleeds resulting in death, minor bleeds) reported in the trials, and using a 60:40 ratio of warfarin to aspirin in the comparator arm.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be greater than 200,000 in Year 5, at an estimated net cost per year to the Government of greater than $100 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC considered the proposed restriction would be difficult to implement. The proposal did not specify how patients would be defined as being "inadequately controlled on warfarin or not suitable for warfarin" in terms of factors such as age, duration of previous warfarin therapy, previous response to warfarin (both effects and adverse effects) or other risk factors that might preclude warfarin treatment. It would therefore be subject to wide variation in interpretation.

The submission nominated warfarin and aspirin as the main comparators. Given that the requested restriction was for patients inadequately controlled on warfarin or for whom warfarin is not suitable, the PBAC considered that aspirin was the more appropriate comparator. The PBAC noted, however, that aspirin is not the appropriate therapy for patients with a $CHADS_2$ score of greater than or equal to two and therefore the selection of

the comparator might need to include consideration of different risk scores of different groups of patients. The PBAC considered that dabigatran may also be a relevant comparator.

The submission presented a post hoc subgroup analysis of patients who had a time in therapeutic range (TTR) with warfarin treatment below the median reported in the ROCKET trial against the entire rivaroxaban treatment arm in ROCKET. ROCKET is a randomised trial comparing rivaroxaban 20 mg per day (patients with moderate renal function received 15 mg per day) with dose-adjusted warfarin in patients with non-valvular atrial fibrillation with at least two risk factors for stroke (the equivalent of a $CHADS_2$ score of greater than or equal to two). The submission presented this subgroup analysis to represent the patient population in the requested restriction of patients who are not adequately controlled on warfarin. The PBAC considered that the subgroup of below median TTR was not representative of the requested PBS population and that the results from the subgroup analysis which was based on post-hoc drug response were not valid. The PBAC noted that the subgroups were not defined by pre-randomisation characteristics. As warfarin was probably not a relevant comparator for the group targeted in the proposed restriction, the PBAC was not able to interpret the submission's claim of superior efficacy and safety of rivaroxaban over warfarin based on this analysis.

The submission also presented a meta-analysis of ten randomised trials comparing aspirin (75-325 mg per day) with dose adjusted warfarin in patients with non-valvular atrial fibrillation (NVAF) (no additional requirement for stroke risk factors were reported). The submission then presented an indirect comparison of the ROCKET trial and the meta-analyses of the warfarin versus aspirin trials to inform the efficacy and safety of rivaroxaban versus aspirin.

The PBAC noted the ESC advice that the indirect comparison of rivaroxaban and aspirin should be interpreted cautiously as the comparability of the trials included in the analysis is questionable, given the stroke risk of patients enrolled, the years over which the trials were conducted and the potential that standard management of patients with AF may have changed over the period of time that the aspirin and ROCKET trials were conducted. The PBAC concurred with ESC that the claims that rivaroxaban is superior in terms of comparative effectiveness and equivalent in terms of comparative safety over aspirin, are not adequately supported by the data presented in the re-submission.

The submission presented a cost utility analysis based on the claim of superior efficacy and safety versus warfarin and superior efficacy and equivalent safety compared with aspirin. The PBAC considered that the economic analysis using the event rates from the ITT analysis for rivaroxaban and subgroup analysis rates from the below median TTR from the ROCKET trial was not appropriate considering the methodological and clinical issues with the analysis outlined above. The model produced an ICER of less than $15,000 per QALY over 20 years based on several outcomes (ischaemic and haemorrhagic stroke, non-CNS embolism, haemoglobin/haematocrit drop, transfusion, critical organ bleeds, major bleeds resulting in death, minor bleeds) reported in the trials, and using a 60:40 ratio of warfarin to aspirin in the comparator arm. The PBAC was unable to interpret this estimate in the context of the proposed population for the PBS restriction.

The PBAC considered that the utilisation estimates in the submission were highly uncertain given that the proposed PBS population of those who are inadequately controlled or for

whom warfarin is not suitable was not defined. The PBAC noted that the estimates also included patients who are not currently treated with warfarin, but in whom warfarin is not contraindicated. The PBAC also considered that there was potential for use beyond the requested restriction in patients with a $CHADS_2$ score of one.

The PBAC therefore rejected the submission on the basis that the subgroup analysis did not provide a basis to support the claim of superior efficacy and safety of rivaroxaban in the proposed population and hence that the cost effectiveness analysis presented was not valid.

The PBAC noted the opportunity cost of listing rivaroxaban for NVAF.

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

The sponsor did not provide further comment.

ADDENDUM – MARCH 2013

STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION REVIEW

Product: Rivaroxaban, tablets, 15 mg and 20 mg, Xarelto®
Sponsor: Bayer Australia 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.

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.

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 varied 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 rivaroxaban was between $15,000 and $45,000 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 rivaroxaban was lower, but also within the range of $15,000 - $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

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 considered that the modelled economic evaluation presented in the minor submission, which included a lower price in comparison to November 2012, to be acceptable for decision making purposes. The PBAC recalled that its previous concerns in relation to the cost-utility analyses presented by rivaroxaban in November 2012 stemmed from clinical issues in relation to event rates and sub-group analysis rates, which flowed onto the economic analysis, rather than methodological problems in the modelling approach. These concerns have been resolved through the new analyses undertaken in the minor submission and during the evaluation.

The PBAC considered that, given the substantial size of the potential patient population and the corresponding number of telephone Authority applications to the Department of Human Services, it did not consider an Authority Required listing to be practically implementable. The PBAC therefore recommended that rivaroxaban be listed as an Authority Required (Streamlined) listing.

The PBAC further 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	№.of Rpts	Proprietary Name and Manufacturer	
RIVAROXABAN			Xarelto	BN
Rivaroxaban 15 mg tablet, 28	1	5		
Rivaroxaban 20 mg tablet, 28	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: 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 ≤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

Bayer welcomes the PBAC's decision to recommend extending the PBS listing of Xarelto. Bayer will continue to work collaboratively with the department of health and aging to bring innovative and cost-effective therapies to Australian patients."