PUBLIC SUMMARY DOCUMENT
Product: Rivaroxaban, tablet, 10 mg, Xarelto®
Sponsor: Bayer Australia Limited
Date of PBAC Consideration: March 2009

1. Purpose of Application

The submission sought a section 85 Authority required (Streamlined) listing and a section 100 (s100) Private Hospital Authority required listing for rivaroxaban for prevention of venous thromboembolism (VTE) in a patient undergoing hip or knee replacement.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate facilities.

2. Background

This was the first time rivaroxaban had been considered by the PBAC.

3. Registration Status

Rivaroxaban was TGA registered on 24 November 2008 for the 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 5 weeks; elective total knee replacement, treatment for up to 2 weeks).

4. Listing Requested and PBAC's View

Section 85 Authority Required (STREAMLINED)
For the prevention of venous thromboembolism in an adult patient undergoing elective total hip replacement surgery (treatment for up to 5 weeks);
For the prevention of venous thromboembolism in an adult patient undergoing elective total knee replacement surgery, (treatment for up to 2 weeks).

Section100 (Highly Specialised Drug)
Private hospital authority required
For the prevention of venous thromboembolism in an adult patient undergoing elective total hip replacement surgery (treatment for up to 5 weeks);
For the prevention of venous thromboembolism in an adult patient undergoing elective total knee replacement surgery, (treatment for up to 2 weeks).

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Rivaroxaban will provide an oral alternative to the currently available injectable anti-thrombotic drugs used to prevent venous thromboembolism (VTE) in patients who have undergone major orthopaedic surgery of the lower limb (total hip or knee replacement).

6. Comparator

The submission nominated enoxaparin as the main comparator. The PBAC accepted this as appropriate.

7. Clinical Trials

The submission presented two randomised key trials to support the listing of rivaroxaban for total hip replacement and one randomised trial to support the listing of rivaroxaban for total knee replacement, as follows:

Total hip replacement:

- RECORD 1: comparing rivaroxaban 10 mg for 35 days with enoxaparin 40 mg for 35 days, consistent with current best practice; and
- RECORD 2: comparing rivaroxaban 10 mg for 35 days with enoxaparin 40 mg for 12 ± 2 days

Total knee replacement:

- RECORD 3: comparing rivaroxaban 10 mg for 12 ± 2 days with enoxaparin 40 mg for 13 ± 2 days, consistent with both current and best practice.

The PBAC agreed that the duration of enoxaparin use in the trials submitted (medians ranged from 13 to 36 days in hip replacement and 13 days in knee replacement) reflected the range of durations in Australian practice.

The trials published at the time of the submission, are as follows:

Trial/First author	Protocol title	PublicationCitation
Direct randomised trial(s)		
RECORD 1		
Eriksson, B. et al	Oral Rivaroxaban Compared with Subcutaneous Enoxaparin for Extended Thromboprophylaxis after Total Hip Arthroplasty: The RECORD1 Trial.	ASH Annual Meeting Abstracts 2007, vol. 110, no. 11, Abstract 6, 2007.
Eriksson, B. et al	Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty.	New England Journal of Medicine, 358(26): 2765-2775, 2008.
RECORD 2		
Kakkar A. K. et al. 2007	Extended Thromboprophylaxis with Rivaroxaban Compared with Short-Term Thromboprophylaxis with Enoxaparin after Total Hip Arthroplasty: The RECORD 2 Trial.	ASH Annual Meeting Abstracts 2007, vol. 110, no. 11, Abstract 307.
RECORD 3		
Lassen M. R, et al	Rivaroxaban - An Oral, Direct Factor Xa Inhibitor - for Thromboprophylaxis after Total Knee Arthroplasty: The RECORD3 Trial.	ASH Annual Meeting Abstracts 2007, vol. 110, no. 11, Abstract 308.
Lassen M. R, et al	Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty.	New England Journal of Medicine, 358(26): 2776-2786, 2008.

ASH=American Society of Hematology; DVT=deep vein thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism.

8. Results of Trials

The results of the trials and associated reports presented in the submission are described below:

Total hip replacement
The results for the primary composite outcome, total VTE, in RECORD 1 and RECORD 2, demonstrated that rivaroxaban was significantly superior in efficacy to enoxaparin in the prevention of VTE in adult patients undergoing elective total hip replacement over the duration of the trial (median time of 13 to 36 days). The disaggregated components of this endpoint also favoured rivaroxaban. The PBAC noted the observed risk difference in each of the trials (RECORD 1: -2.6%, 95%CI -3.7%, -1.5%; RECORD 2: -7.3%, 95%CI -9.4%, -5.2%) was likely to be significant given the incidence of total VTE in the comparator group of 3.7% and 9.3% for RECORD 1 and RECORD 2 respectively.

Total knee replacement
The results for the primary composite outcome, total VTE, in RECORD 3 demonstrated that rivaroxaban was significantly superior in efficacy to enoxaparin in the prevention of VTE in adult patients undergoing elective total knee replacement over the duration of the trial (median time of 13 days). The observed risk difference (-9.2%, 95% CI -12.4%, -5.9%) was likely to be regarded as clinically significant given the incidence of total VTE in the enoxaparin treatment group was 18.9%.

The PBAC noted the results for total VTE in all three trials were heavily weighted by the larger proportion of asymptomatic deep vein thrombosis (DVT) and distal DVT. However, the secondary composite outcome measures, which excluded all distal DVT, also supported the superior efficacy of rivaroxaban over enoxaparin in patients undergoing total hip replacement (THR) and total knee replacement (TKR).

Between 30-35% of randomised participants were excluded from the analysis of the primary outcome in each of the trials. The main reason for exclusion was inadequate assessment (either no venography or unilateral or non-evaluable venography). Excluded participants were evenly distributed between treatment groups in all of the trials and the reasons for exclusion were also similar between groups. Comparison of the baseline characteristics between the safety population and the primary efficacy analysis set for each trial failed to detect any differential loss to follow-up between the treatment groups.

The primary outcome for all of the RECORD trials was total VTE, a composite endpoint including any symptomatic or asymptomatic DVT (proximal and/or distal), non-fatal pulmonary embolism (PE), and death from all causes. The PBAC noted the recommendation in current international guidelines is to use a composite, including all proximal DVT, symptomatic non-fatal pulmonary embolism (PE), VTE related death or death due to any cause, ± symptomatic distal DVT. Asymptomatic distal DVT was not included in the recommended composite endpoints in these guidelines. Although the primary composite outcome in all three trials included asymptomatic distal DVT, both the disaggregated components of this endpoint, and a number of secondary composite outcomes which did not include all distal DVT, supported the superiority of rivaroxaban over enoxaparin in all of the trials included in the submission.

The submission provided data on the incidence of treatment-emergent major bleeding and a summary of other adverse events in each of the RECORD trials. The safety of prolonged use of rivaroxaban has not been evaluated.

A summary of the treatment emergent bleeding events in the direct randomised trials is shown in the table below:

Trial ID	Rivaroxaban n with event/N (%)	Enoxaparin n with event/N (%)	Risk Difference RD % (95%CI)	RR (95% CI)
Total hip replacement				
RECORD 1				
Major bleeding[a]	6/2209 (0.3)	2/2224 (<0.1)	0.18 (-0.07,0.43)	3.02 (0.61,15.0)
Any bleeding	133/2209 (6.0)	131/2224 (5.9)	0.13 (-1.26,1.52)	1.02 (0.81,1.29)
Clinically relevant bleeding	70/2209 (3.2)	56/2224 (2.5)	0.65 (-0.33,1.63)	1.26 (0.89,1.78)
Non major bleeding	128/2209 (5.2)	129/2224 (5.8)	-0.01(-1.38,1.37)	1.00 (0.79,1.27)
Non major clinically relevant bleeding	65/2209 (2.9)	54/2224 (2.4)	0.51(-0.44,1.47)	1.21 (0.85,1.73)
Other non major bleeding	71/2209 (3.2)	77/2224 (3.5)	-0.25 (-1.31,0.81)	0.93 (0.68,1.28)
Major bleeding including surgical site bleeding[b]	40/2209 (1.8)	33/2224 (1.5)	0.33 (-0.42,1.08)	1.22 (0.77,1.93)
RECORD 2				
Major bleeding[a]	1/1228 (<0.1)	1/1229 (<0.1)	0.00 (-0.00 0.00)	1.00 (0.06,5.98)
Any bleeding	81/1228 (6.6)	68/1229 (5.5)	1.06 (-0.82,2.95)	1.19 (0.87,1.63)
Clinically relevant bleeding	41/1228 (3.3)	34/1229 (2.8)	0.57 (-0.79,1.93)	1.21 (0.77,1.89)
Non major bleeding	80/1228 (6.5)	67/1229 (5.5)	1.06 (-0.81,2.94)	1.20 (0.87,1.64)
Non major clinically relevant bleeding	40/1228 (3.3)	33/1229 (2.7)	0.57 (-0.77,1.91)	1.21 (0.77,1.91)
Other non major bleeding	43/1228 (3.5)	36/1229 (2.9)	0.57 (-0.82,1.97)	1.20 (0.77,1.85)
Major bleeding including surgical site bleeding[b]	23/1228 (1.9)	19/1229 (1.6)	0.33 (-0.70,1.35)	1.21 (0.66,2.21)
Total knee replacement				
RECORD 3				
Major bleeding[a]	7/1220 (0.6)	6/1239 (0.5)	0.09 (-0.48,0.66)	1.18 (0.40,3.52)
Any bleeding	60/1220 (4.9)	60/1239 (4.8)	0.08 (-1.63,1.78)	1.02 (0.72,1.44)
Clinically relevant bleeding	40/1220 (3.3)	34/1239 (2.7)	0.53 (-0.82,1.89)	1.19 (0.76,1.87)
Non major bleeding	53/1220 (4.3)	54/1239 (4.4)	-0.01 (-1.63,1.60)	1.00 (0.69,1.44)
Non major clinically relevant bleeding	33/1220 (2.7)	28/1239 (2.3)	0.45 (-0.79,1.68)	1.20 (0.73,1.97)
Other non major bleeding	22/1220 (1.8)	31/1239 (2.5)	-0.70 (-1.85,0.45)	0.72 (0.42,1.24)
Major bleeding including surgical site bleeding[b]	21/1220 (1.7)	17/1239 (1.4)	0.35 (-0.63,1.33)	1.25 (0.67,2.37)

RR=relative risk.

[a] Primary safety outcome. This outcome does not include bleeding at the surgical site.

[b] Incidence of treatment emergent major bleeding events after removing the restriction to extra-surgical site for those bleeding events associated with a fall in haemoglobin of ≥2g/dL or for those bleeding events leading to transfusions of ≥2units of whole blood or packed cells.

The incidence of major bleeding in the trials in patients undergoing THR (RECORD 1 & 2) was low for both drugs (< 0.1 – 0.31) and there was no statistically significant difference between the rivaroxaban and enoxaparin treatment groups in either trial. The PBAC noted trials were underpowered for detecting any statistically significant difference in the rate of

treatment-emergent major bleeding events. The PBAC also noted there were insufficient data to determine accurately the comparative incidence of cardiovascular events for the two drugs. Minimal information was available regarding the potential effect of rivaroxaban on hepatic and renal function or the potential for other rare or delayed adverse events. There were no safety data for patient groups other than those undergoing elective total hip replacement and elective total knee replacement.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that rivaroxaban was superior in terms of comparative effectiveness and equivalent in terms of comparative safety over enoxaparin for prevention of VTE in patients undergoing elective total hip replacement and elective total knee replacement.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A modelled economic evaluation was presented. The type of economic evaluation presented was a cost-utility analysis with a 5.25 years time horizon.

The outcomes used in the economic evaluation were years of life (YoL) gained and quality-adjusted life-years (QALYs) gained. An individual patient level simulation was used to generate the results.

The model based on RECORD 1 was driven by the transition probabilities in the extrapolation period and consequent costs of diagnosis and treatment of long-term complications, as well as their utilities. Risks of recurrent VTE and of post-thrombotic syndrome (PTS) after symptomatic DVT were not derived from the population for whom PBS listing is sought. Utilities values were derived from varied population using varied methods.

Compared with the model based on RECORD 1, the model based on RECORD 2 was more significantly driven by age-stratified VTE rates and the long term extrapolations.

The trial-based economic evaluation using RECORD 1 and RECORD 2 resulted in an incremental cost-effectiveness ratio (ICER) of up to $75,000 per QALY dependent on the inclusion of symptomatic, asymptomatic, recurrent VTE, PTS and pulmonary embolism (PE) complications. The ICER for RECORD 1 and RECORD 2 dropped to between $15,000 - $45,000 and less than $15,000, respectively, following the inclusion of the risk reduction for recurrent VTE and long-term complications in the economic evaluation.

With respect to RECORD 3, the preliminary economic evaluation resulted in an ICER of between $105,000 – $200,000 per QALY. However, in the stepped economic evaluation, an ICER in the range of $15,000 - $45,000 accounting for a risk reduction in the conversion of asymptomatic to symptomatic VTE within 90-days post surgery in the economic evaluation was calculated. Rivaroxaban was more effective and less costly than enoxaparin if the risk of post-thrombotic syndrome (PTS) in the long term for asymptomatic patients, and pulmonary embolism (PE) case fatality rate in the long term were accounted for in the economic model.

The economic evaluation showed that the utility values and the conversion from asymptomatic to symptomatic VTE and its long-term complications appeared to drive the model in demonstrating the greater effectiveness and lower cost of rivaroxaban over enoxaparin.

In all three models, the incremental gains in years of life and quality-adjusted life-years were minimal, which resulted in an ICER sensitive to small changes in both costs and effectiveness.

Sensitivity analyses indicated that the model was sensitive to the proportion of people who needed home nursing to assist with enoxaparin injection, as well as the transition probabilities between VTE and its long term extrapolations, all of which were subject to uncertainty.

The time horizon played an important role in the ICER calculation. In the model based on each of the RECORD trials, the incremental cost/YoL and incremental cost/QALY decreased dramatically from Year 0.25 to Year 5.25, even in the absence of extrapolation of long term events.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients/year expected to receive rivaroxaban for total hip and knee replacement would be between 50,000 – 100,000 in Year 5, with a financial cost/year to the PBS of < $10 million.

The submission's estimates however were considered an approximation due to uncertainty regarding the expected rate of uptake of rivaroxaban and the current level of use of enoxaparin for this indication.

12. Recommendation and Reasons

The PBAC recommended 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. Listing under section 100 was not recommended as rivaroxaban does not meet all five selection criteria. The maximum quantities should align with the pack sizes and the Therapeutic Goods Administration (TGA)-recommended durations of use (five weeks for hip replacement and two weeks for knee replacement) to minimise wastage. The PBAC noted that the quantities to be subsidised by the PBS would differ according to whether the therapy is initiated in the public hospital setting or the private hospital setting.

The PBAC agreed that subcutaneous enoxaparin was the appropriate main comparator, and that the duration of its use in the trials submitted (medians ranged from 13 to 36 days in hip replacement and 13 days in knee replacement) reflected the range of durations in Australian practice.

The primary outcome analysed in the randomised trials was a composite measure which was dominated by a relatively large number of asymptomatic events detected by venography that had no direct patient relevance (especially asymptomatic distal deep vein thromboses). Across the trials, there were 30% to 35% of patients who were not assessed for this primary outcome mainly due to problems with venography, but loss to follow-up was similar across the arms of each trial. Thus the conclusion for superior effectiveness rested on a reckoning

that the composite outcome results reflected the results for each of the rarer and directly patient-relevant types of events included in the composite outcome.

The PBAC was concerned that the point estimates for treatment-emergent bleeding, although not statistically significant, tended to favour enoxaparin over rivaroxaban. This is of concern because of the potential of increasing clinically important bleeding; the exclusion of surgical site bleeding from the definition of "major bleeding" unless also associated with haemoglobin changes and/or requiring transfusion; the paucity of evidence available in the extended assessment of harms; the likelihood that these trials were underpowered to detect this outcome; and the lack of an accepted asymptomatic endpoint or measure that is more commonly occurring and can predict these rare events.

The PBAC noted that, despite concerns with the use of (a) utilities from across multiple sources, and (b) transition probabilities between events derived from non-surgical patients, the economic evaluation was relatively robust to these sources of uncertainty. The incremental cost-effectiveness ratio was most sensitive to the time horizon. reflected by the large reduction in the ICER from the 0.25-year duration of follow-up in the trials to the 5.25-year duration of the modelled economic evaluation. This reflects the sensitivity of the economic evaluation both to small differences in the major clinical outcomes of pulmonary emboli and deaths and also to the justified inclusion of recurrent venous thrombotic events and the post-thrombotic syndrome.

The PBAC concluded that oral rivaroxaban 10 mg once daily was more effective, but possibly less safe, than subcutaneous enoxaparin 40 mg once daily in the restrictions requested for PBS listing and across the range of durations of use of enoxaparin currently used in Australia. The Committee recommended listing on the basis of uncertain but overall acceptable cost-effectiveness.

The PBAC suggested that the NPS consider providing a RADAR suitable for consumers as well as a RADAR suitable for health professionals.

Recommendation:
RIVAROXABAN, tablet, 10 mg, 15 tablet pack, 30 tablet pack

Restriction:	<u>Authority Required</u> Prevention of venous thromboembolism in a patient undergoing total hip replacement.
Max Qty:	10, 1(15 tablet pack), 1(30 tablet pack)
Repeats:	1(10 tablets), 1(15 tablet pack), nil (30 tablet pack)
	NOTE: No applications for increased maximum quantity and/or repeats will be authorised for the 30 tablet pack
	<u>Authority Required</u> Prevention of venous thromboembolism in a patient undergoing total knee replacement.

Max Qty: 10, 1(15 tablet pack)
Repeats: nil

NOTE:
No applications for increased maximum quantities and/or repeats will be authorised.

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 is pleased with the positive PBAC recommendation and encourages anyone interested in further discussing the data to contact the company. Bayer does not agree with the PBACs conclusion regarding safety. A published meta-analysis of the RECORD 1-3 trials is now available (post-PBAC) which (addresses this issue and) supports the companies claim of similar safety.