PUBLIC SUMMARY DOCUMENT
Product: Rivaroxaban, tablets, 15mg and 20mg, Xarelto®
Sponsor: Bayer Australia Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application
The application requested the current Authority required (STREAMLINED) listing be extended to include treatment of acute symptomatic pulmonary embolism (PE) and prevention of recurrent venous thromboembolism (VTE).

2. Background
This indication of rivaroxaban had not previously been considered by the PBAC.

3. Registration Status
The application was submitted under the TGA/PBAC parallel process. At the time of PBAC consideration the Clinical Evaluation Report and TGA Delegate's Overview were available.

Rivaroxaban is currently registered by the TGA for the following indications:

- Prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs;
- 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 pulmonary embolism (PE) for the prevention of recurrent DVT and PE.

4. Listing Requested and PBAC's View
Authority required (STREAMLINED)
Initial treatment of confirmed acute symptomatic pulmonary embolism (PE)

Authority Required (STREAMLINED)
Continuing treatment of confirmed acute symptomatic pulmonary embolism (PE), and for the prevention of venous thromboembolism (VTE).

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Rivaroxaban was proposed for the treatment of acute symptomatic PE and prevention of recurrent VTE. Rivaroxaban was not expected to alter the current diagnosis algorithm or determination of duration of treatment for PE, but will be a single drug alternative to enoxaparin/warfarin.

6. Comparator
The submission nominated enoxaparin 80mg twice daily followed by INR adjusted warfarin as the comparator. This was accepted by the PBAC.

7. Clinical Trials
The submission presented one randomised trial (EINSTEIN-PE) comparing rivaroxaban with enoxaparin/warfarin at equi-effective doses followed by vitamin K antagonist (VKA), in 4,833 patients with acute symptomatic pulmonary embolism (PE) with or without deep-vein thrombosis (DVT).

The submission also presented a meta-analysis of the EINSTEIN-PE and EINSTEIN-DVT trial, the latter previously considered by the PBAC in seeking listing of rivaroxaban for the treatment of DVT (Refer to the March 2012 Public Summary Document for publication details of EINSTEIN-DVT).

For PBAC's view, see Recommendation & Reasons.

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
EINSTEIN-PE Buller HR, et al.	Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism	The New England Journal of Medicine 2012; 366 (14): 1287-97

8. Results of Trials

The primary effectiveness outcome in EINSTEIN-PE was recurrent VTE, i.e. the composite of recurrent DVT or non-fatal or fatal PE.

Compared to enoxaparin/VKA, treatment with rivaroxaban was associated with a numerically higher but not statistically significant hazard of symptomatic DVT or fatal/non-fatal PE (HR (95%CI): 1.123 (0.749, 1.684) in the intention-to-treat (ITT) population and 1.066 (0.697, 1.632) in the per protocol (PP) population. Absolute risk differences (95% CI) of the increased risk of VTE were 0.24% (-0.55%, 1.04%) and 0.1% (-0.66%, 0.87%) for the ITT and PP populations respectively.

The principle safety outcome for the EINSTEIN-PE trial was 'major bleeding or clinically relevant non-major bleeding'. Overall, the rates of the composite of major bleeding and clinically relevant non-major bleeding were similar between rivaroxaban and enoxaparin/VKA treated patients HR (95%CI): 0.90 (0.758, 1.069). Approximately, 90% of the principle safety events were clinically relevant non-major bleeding events, which was not significantly different between the two treatment arms.

The PBAC noted that although approximately 10% of the principal safety events were major bleeding, this was significantly lower in patients treated with rivaroxaban compared to enoxaparin/VKA ((1.1%) versus (2.2%), RD (95% CI): -1.1 (-1.8, -0.4)). The PBAC noted that this was primarily driven by the reductions in the numbers of intracranial and retroperitoneal bleeds, as the numbers of bleeds from other major sites were similar between the treatments.

For non-major clinically relevant bleeding, although the overall event rate did not differ between the treatments, the numbers of gastrointestinal bleeds were significantly higher in the rivaroxaban treatment arm (1.6% versus 0.7% RD [95% CI]: 0.9 [0.3, 1.5]), but the number of bleeds from injection sites were lower with rivaroxaban (<0.1% versus 0.4%, RD [95% CI]: -0.4 [-0.4,-0.1]). The PBAC noted the similarity in incidences of all other non-major clinically relevant bleeds.

The PBAC also noted that the numbers of bleeding events leading to permanent discontinuation of study drug were similar between the treatment arms.

For PBAC's view, see Recommendation & Reasons.

9. Clinical Claim

The submission claimed rivaroxaban as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over enoxaparin and INR adjusted VKA therapy.

For PBAC's view, see Recommendation & Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on the claim of non-inferiority for recurrent VTE, i.e. the composite of recurrent DVT or non-fatal or fatal PE outcome, and included additional costs/offsets for length of hospitalisation, drug monitoring costs (INR tests) and costs of managing adverse events (intracranial and extracranial bleeds).

The PBAC recalled that the warfarin dose was higher by 0.5 mg than the dose used for rivaroxaban for treatment of DVT. The PBAC noted that the current submission claimed that this was due to more accurate testing and based on data from patient diaries. The PBAC considered that although this may be reasonable, the higher warfarin dose increases the cost of rivaroxaban by a proportionate amount.

The PBAC acknowledged the cost of rivaroxaban was driven by the number of INR tests in patients being treated with warfarin and the length of hospitalisation with rivaroxaban compared with enoxaparin/warfarin. The PBAC considered the different treatment requirements of PE compared to DVT and considered that the assumed number of INR tests for PE was probably reasonable, although high.

The PBAC considered the claimed half-day savings in length of hospital stay would be health system dependent. Specifically, the PBAC considered that in the case of hospitals with well-established mechanisms to manage patients being stabilised on warfarin outside the inpatient setting (e.g. "hospital-in-the-home" arrangements) patients would be unlikely to have an extended stay in hospital. This would therefore reduce the likelihood of observing an incremental benefit in terms of hospitalisation time for rivaroxaban. The PBAC noted also that some patients undergoing warfarin stabilisation may do so in the community setting and that patients who do attend hospital may do so for other reasons aside from monitoring of anticoagulation, therefore these hospital stays would not be avoided for patients on rivaroxaban. The PBAC therefore considered that the projected savings in hospitalisation time may not translate into Australian clinical practice, and that claims of cost savings were not adequately supported.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $ 10 million in Year 5.

For PBAC's view, see Recommendation & Reasons.

12. Recommendation and Reasons

The PBAC recommended the current Authority required (STREAMLINED) listing be extended to include treatment of acute symptomatic pulmonary embolism (PE) and prevention of recurrent venous thromboembolism (VTE), on a cost minimisation basis compared with enoxaparin 80 mg twice daily followed by INR adjusted warfarin, at same treatment cost for enoxaparin 80mg twice daily followed by INR adjusted warfarin.

The PBAC considered the dosing protocol used in EINSTEIN-PE was consistent with use of enoxaparin in clinical practice, with the exception of use of enoxaparin at a once daily dose of 1.5 mg/kg in early discharge programs. The PBAC noted that the trial's open label design as a potential source of bias, however overall the PBAC considered the results of acceptable reliability.

The PBAC considered the presented trial results indicated rivaroxaban was non-inferior to enoxaparin/VKA for the treatment of acute PE on the basis of the submission's non-inferiority margin (the upper 95%CI for the hazard ratio (HR) of 2) and minimally clinically important difference (MCID) (an increase in absolute risk VTE of less than 1.26%).

The PBAC further considered whether the submission's derivation of non-inferiority margin and the MCID were meaningful and appropriate. The issue was whether the observed upper 95% CIs from the EINSTEIN-PE trial for the primary efficacy outcome of the recurrent DVT or nonfatal/fatal PE, at an HR of 1.684 and an absolute risk difference of 1.04% in ITT populations, were likely to include clinically relevant outcomes. The PBAC accepted the sponsor's derivation of the non-inferiority margins.

The PBAC did not accept the cost offsets for reduced length of hospitalisations presented by the submission, as it considered that there was insufficient evidence to support claims of shortened hospital stay. The realisation of the cost savings as a consequence of this assumption was considered to be dependent on the particular hospital system and may not in reality, translate into clinical practice. The estimated frequency of INR tests was accepted by the PBAC, based on expert clinical advice from a vascular physician involved in both the EINSTEIN-DVT and EINSTEIN PE trials, and likely clinical practice.

The PBAC accepted the submission's claim that rivaroxaban is non-inferior in terms of clinical effectiveness compared to enoxaparin/VKA in the treatment of acute PE. In terms of comparative safety, the PBAC agreed with the submission's claims of superiority over enoxaparin and INR adjusted VKA therapy.

The PBAC considered the potential for usage beyond the requested restriction, particularly in patients with PE who are haemodynamically unstable or with chronic thromboembolic disease. It accepted that these patients groups were likely to be small and recommended that the restriction not be confined to the trial population.

The PBAC was concerned that current prescribing software packages and listings of item numbers generated different listings with different costs. Practically, this may result in wrong indications being chosen and drug costs may increase as a consequence of selecting the wrong streamlined code. The PBAC suggested that DUSC may wish to monitor usage and this information be used to inform consideration as to how to manage total cost. The PBAC considered the greatest uncertainty in usage is the number of patients that may switch from warfarin to rivaroxaban.

The PBAC noted that rivaroxaban was already included in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements under a shared care model.

Recommendation:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
RIVAROXABAN rivaroxaban 15 mg tablet, 42	1	0	Xarelto	BN

Condition/Indication:	Pulmonary embolism
Treatment phase:	Initial treatment
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	Patient must have confirmed acute symptomatic pulmonary embolism
Administrative Advice	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. No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised

RIVAROXABAN rivaroxaban 20 mg tablet, 28	1	5	Xarelto	BN

Condition/Indication:	Pulmonary embolism
Treatment phase:	Continuing treatment
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	Patient must have confirmed acute symptomatic pulmonary embolism.
Administrative Advice	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. No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may 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 welcomes the PBAC's decision to recommend extending the PBS listing of Xarelto to include the treatment of acute symptomatic PE and the prevention of recurrent VTE. Bayer will continue to work collaboratively with the department of health and aging to bring innovative therapies to Australian patients.