6.09 RIVAROXABAN, Tablet, 10 mg, Xarelto®, Bayer Australia Limited

1 Purpose of Application

1.1 The submission requested extending the listing of rivaroxaban 10mg to include an Authority Required (STREAMLINED) listing for the prevention of recurrent venous thromboembolism (VTE).

1.2 The basis for the submission was a cost-minimisation analysis against rivaroxaban 20 mg and apixaban 2.5 mg, informed by a direct comparison between rivaroxaban 10 mg and rivaroxaban 20 mg (Einstein CHOICE), and an indirect treatment comparison (ITC) between rivaroxaban 10 mg and apixaban 2.5 mg. The key components of the submission are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adults with a history of VTE.
Intervention	Extended treatment with rivaroxaban 10 mg once daily for prevention of VTE recurrence.
Comparator	1) Prevention of VTE recurrence with rivaroxaban 20 mg once daily. 2) Prevention of VTE recurrence with apixaban 2.5 mg twice daily.
Outcomes	Efficacy: VTE-related mortality, VTE recurrence. Safety: major bleeding, clinically relevant nonmajor bleeding (CRNM), serious adverse events.
Clinical claim	In adults with a history of VTE, prevention of recurrent VTE with rivaroxaban 10 mg once daily is therapeutically equivalent to: • Rivaroxaban 20 mg once daily in terms of the risk of VTE recurrence and VTE-related death, whilst offering a slightly better safety profile in terms of major and CRNM bleeding; and • Apixaban 2.5 mg twice daily in terms of the risk of recurrent VTE and VTE-related death, major and CRNM bleeding. The clinical and safety claims were supported by the evidence presented in the submission.

Source: Table 1.1, p2 of the submission
Abbreviations: CRNM=clinically relevant nonmajor; VTE=venous thromboembolism

2 Requested listing

2.1 The proposed listing was consistent with the clinical and economic evidence presented in the submission and the PBS restrictions applied to the comparators (rivaroxaban 20 mg and apixaban 2.5 mg) for the prevention of recurrent VTE. The proposed PBS listing is presented in the table below.

2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
RIVAROXABAN 10 mg tablet, 30	1	5	$92.74 (published) $[redacted] (effective)	Xarelto®	Bayer Australia Limited

Category / Program	*GENERAL – General Schedule (Code GE)*
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Prevention of recurrent venous thromboembolism
PBS Indication:	Prevention of recurrent venous thromboembolism
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have a history of venous thromboembolism.
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.* ***Note*** ***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.* *Special Pricing Arrangements apply.*

2.3 The submission acknowledged that rivaroxaban 20 mg is listed under a special pricing arrangement (SPA). Accordingly, the submission proposed that it would accept the cost-minimising price resulting from applying the estimated dose relativity between rivaroxaban 10 mg and rivaroxaban 20 mg and the same SPA (via a confidential rebate of [redacted]%) to calculate the effective price for rivaroxaban 10 mg.

3 Background

3.1 Rivaroxaban 10 mg was listed on the ARTG on 18 September 2018 for prevention of recurrent VTE. The Product Information states that "Following completion of six to twelve months therapy, based on an individual assessment of the risk of recurrent DVT or PE against the risk for bleeding, dose reduction to 10 mg Xarelto once daily may be considered".

3.2 This is the first submission to the PBAC requesting listing of rivaroxaban 10 mg for the prevention of recurrent venous thromboembolism (VTE; Authority Required Code 4132).

4 Population and disease

4.1 VTE comprises deep venous thrombosis (DVT) and pulmonary embolism (PE). It has a high risk of recurrence, can impair patients' quality of life, and is associated with significant morbidity and mortality. VTE is usually classified according to whether it has been provoked (is associated with underlying risk factors) or unprovoked (occurrence in the absence of underlying risk factors). Approximately 50% of VTE patients experience unprovoked events.

4.2 The submission proposed the use of rivaroxaban 10 mg as a treatment alternative to rivaroxaban 20 mg or apixaban 2.5 mg for prevention of VTE in adults with unprovoked VTE at high risk of a recurrence, or in those with provoked VTE who have a persistent provoking factor other than cancer. This was appropriate.

5 Comparator

5.1 The submission nominated rivaroxaban 20 mg (2268J) and apixaban 2.5 mg (2744K) as the main clinical comparators. These comparators are appropriate given that: (1) rivaroxaban 10 mg is intended to provide a lower strength alternative to rivaroxaban 20 mg in patients requiring VTE prophylaxis; (2) they are from the same pharmacological group of therapies (direct acting factor Xa inhibitors); and (3) these are the only treatments for prevention of VTE (Authority Code 4132) currently listed on the PBS. The Pre-PBAC Response stated that dose flexibility is relevant in this indication, and that apixaban does not offer dose flexibility.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no sponsor hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on one head-to-head trial comparing rivaroxaban 10 mg to rivaroxaban 20 mg (Einstein CHOICE) and an ITC of rivaroxaban 10 mg and apixaban 2.5 mg; via aspirin and placebo, and via rivaroxaban 20 mg and placebo, as common comparators. This was appropriate. The submission presented three direct randomised controlled trials containing either rivaroxaban or apixaban (RCTs; Einstein CHOICE, Einstein EXT and Amplify EXT) and two RCTs (WARFSA and ASPIRE) sourced from one meta-analysis (Robertson 2017) used as the basis of the ITC. No other relevant studies were identified.

6.4 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Einstein CHOICE	CSR Einstein CHOICE: Reduced-dosed rivaroxaban and standard-dosed rivaroxaban verses ASA in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis and/or pulmonary embolism. The Einstein CHOICE study	Sponsor internal database February 2017
	Weitz J, Lensing A, Prins M, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism.	New England Journal of Medicine. 2017;376(13):1211-1222
	Reduced-dosed rivaroxaban in the long-term prevention of recurrent symptomatic VTE (venous thromboembolism) (Einstein Choice). NCT02064439	Registry search
	Reduced-dosed rivaroxaban and standard-dosed rivaroxaban verses ASA in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis and/or pulmonary embolism. The Einstein CHOICE study. EudraCT Number: 2013-000619-26	Registry search
Einstein EXT	CSR Einstein EXT 1 Sept 2010 (Sponsor on file): Once-daily oral direct factor Xa inhibitor rivaroxaban in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis or pulmonary embolism. The Einstein extension study.	Sponsor on file September 2010
	Einstein Investigators, Bauersachs R, Brenner B, Buller H, et al. Oral rivaroxaban for symptomatic venous thromboembolism.	New England Journal of Medicine. 2010;363(26):2499-2510
	Once daily direct factor Xa inhibitor rivaroxaban in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis or pulmonary embolism. The Einstein-Extension study. NCT00439725	Registry search
	Once daily direct factor Xa inhibitor rivaroxaban in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis or pulmonary embolism. The Einstein-Extension study. Eudract_number:2006-004494-96.	Registry search
Amplify EXT	Agnelli G, Buller H, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism.	New England Journal of Medicine. 2013;368(8).699-708.
	Liu X, Thompson J, Phatak H, et al. Extended anticoagulation with apixaban reduces hospitalisations in patients with venous thromboembolism: An analysis of the AMPLYF-EXT trial.	Thrombosis and Haemostasis. 2016;115(1):161-168.
	Efficacy and safety study of apixaban for extended treatment of deep-vein thrombosis or pulmonary embolism. NCT0063389	Registry search
Robertson 2017	ASPIRE Brighton TA, Ei Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, et al. Low-dose aspirin for preventing recurrent venous thromboembolism.	New England Journal of Medicine 2012;367(21):1979–87
	WARFASA Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, et al. Aspirin for preventing the recurrence of venous thromboembolism.	New England Journal of Medicine 2012;366(21):1959–67

Source: Table 2.6, p31 of the submission, Robertson 2017

Abbreviations: ASA=aspirin; CSR=clinical study report; ID=identification; VTE= venous thromboembolism.

6.5 The key features of the direct randomised trials are summarised in Table 4. All trials were randomised, double-blind studies in patients with VTE. In all trials, the intended treatment duration was up to 12 months. Einstein CHOICE compared the efficacy and safety of rivaroxaban 10 mg, rivaroxaban 20 mg and aspirin. Einstein EXT was a superiority study comparing the efficacy and safety of rivaroxaban 20 mg with placebo. Amplify EXT compared apixaban 2.5 mg with apixaban 5 mg and placebo. The assessment of risk of bias in the main trials presented by the submission was appropriate and the overall risk of bias in the trials was considered low. Details and results from the apixaban 5 mg dose group (Amplify EXT) were not considered in this submission as they were not relevant to the comparisons undertaken. This was appropriate.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Einstein CHOICE	3396	R, DB 12 months	Low	Patients with confirmed symptomatic PE and/or DVT who had been treated for 6 to 12 months and did not interrupt anticoagulation for longer than 1 week	Primary outcomes: - Symptomatic, recurrent fatal or nonfatal VTE - Major bleeding Secondary outcomes: - VTE recurrence, myocardial infraction, ischaemic stroke or systemic embolism - CRNM bleeding
Einstein EXT	1196	R, DB 6 or 12 months	Low	Patients with confirmed symptomatic DVT or PE who had been treated for either - 6 or 12 months with VKA or rivaroxaban in study 11702 or - 6 to 14 months with VKA	Primary outcomes: - Symptomatic, recurrent VTE - Major bleeding Secondary outcomes: - Recurrent VTE and all-cause mortality - CRNM bleeding
Amplify EXT	2486	R, DB 12 months	Low	Patients ≥18 years of age with objectively confirmed, symptomatic proximal DVT or PE (with or without DVT) 3 who had - been treated for 6 to 12 months with standard anticoagulant therapy or - completed treatment with apixaban or enoxaparin and warfarin as participants in the Amplify trial.	Primary outcomes - Symptomatic recurrent VTE or death from any cause; - Major bleeding Secondary outcomes: - Symptomatic recurrent VTE or VTE-related death; - Major or CRNM bleeding

Source: Compiled during evaluation

Abbreviations: CRNM=clinically relevant nonmajor; DB=double blind; DVT=deep venous thrombosis; PE=pulmonary embolism; R=randomised; VTE=venous thromboembolism.

6.6 The key features of the randomised trials included in the meta-analysis (WARFASA and ASPIRE, as sourced from Robertson 2017) are summarised in Table 5. ASPIRE and WARFASA were randomised, double-blind placebo control studies to assess the efficacy and safety of aspirin in patients with unprovoked VTE. The intended treatment duration was 2 years in WARFASA and 4 years in ASPIRE. The submission did not report the results for these trials separately, only as part of the ITC. The risk of bias

assessment of the trials (ASPIRE and WARFASA) reported in Robertson 2017 was moderate due to the high risk of selection bias in WARFASA. The Pre-Sub-Committee Response (PSCR) stated that comprehensive details of WARFASA and ASPIRE were not presented in the submission as "they were only used as "common control" trials in complementary two-step indirect comparisons." The sponsor agreed with the assessment of bias of these trials presented in the evaluation.

Table 5: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
ASPIRE	822	R, DB 4 years	Low	Patients who had a first unprovoked episode of objectively diagnosed symptomatic DVT involving the popliteal vein or more proximal leg veins or an acute PE.	Primary outcomes: - Recurrence of VTE - Major or CRNM bleeding Secondary outcomes: - Major vascular events and a measure of the net clinical benefit
WARFASA	403	R, DB 2 years	Moderate	Patients with first unprovoked VTE who had completed 6-18 months of oral anticoagulant treatment	Primary outcomes: - Symptomatic recurrent of VTE - Major bleeding Secondary outcomes: - Arterial events and all-cause mortality - CRNM bleeding

Source: Compiled during the evaluation
Abbreviations: CRNM=clinically relevant non-major; DB=double blind; DVT=deep venous thrombosis; PE=pulmonary embolism; R=randomised; VTE=venous thromboembolism.

6.7 All five trials were sufficiently comparable in their baseline demographics and disease characteristics, and the methods applied in terms of their study design and analysis of primary efficacy and safety outcomes to justify their inclusion in the ITC.

Comparative effectiveness

6.8 The results for recurrent VTE or VTE-related death are presented in Table 6 and showed statistically significant lower rates of recurrent VTE or VTE-related death for rivaroxaban 10 mg compared with aspirin (Einstein CHOICE), rivaroxaban 20 mg compared with aspirin (Einstein CHOICE) or placebo (Einstein EXT), and apixaban 2.5 mg compared with placebo (Amplify EXT).

6.9 The results of the direct comparison of rivaroxaban 10 mg with rivaroxaban 20 mg showed no significant statistical differences between the two groups.

6.10 The results in WARFASA (used in the ITC) showed a statistically significant reduction in favour of aspirin compared with placebo in the rate of recurrent VTE or VTE-related death. This was not shown in ASPIRE.

Table 6: Results of recurrent VTE or VTE-related death across the trials: dichotomous data

Trial ID	Intervention, n/N (%)	Comparators, n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)
Einstein CHOICE	R10 13/1127 (1.2)	R20 17/1107 (1.5)	0.75 (0.36, 1.54)[2] 0.751 (0.367, 1.539)	-0.004 (-0.013, 0.006)
		ASA 50/1131 (4.4)	**0.26 (0.14, 0.47)**[2] **0.261 (0.143, 0.478)**	**-0.033 (-0.046, -0.019)**
	R20 17/1107 (1.5)	ASA 50/1131 (4.4)	**0.34 (0.20, 0.59)**[2] **0.347 (0.202, 0.598)**	**-0.029 (-0.043, -0.015)**
Einstein EXT	R20 8/602 (1.3)	PBO 42/594 (7.1)	**0.18 (0.09, 0.39)**[2] **0.188 (0.089, 0.397)**	**-0.057 (-0.08, -0.035)**
Amplify EXT[1]	A2.5 14/840 (1.7)	A5 14/813 (1.7)	0.968(0.464, 2.017)	-0.001 (-0.013, 0.012)
		PBO 73/829 (8.8)	**0.189 (0.108, 0.333)**	**-0.071 (-0.093, -0.05)**
	A5 14/813 (1.7)	PBO 73/829 (8.8)	**0.196 (0.111, 0.344)**	**-0.071 (-0.092, -0.05)**
ASPIRE	ASA 57/411 (4.8)	PBO 73/411 (6.5)	0.781 (0.568, 1.073)	-0.039 (-0.089, 0.011)
WARFASA	ASA 28/205 (13.6)	PBO 43/197 (21.8)	**0.626 (0.405, 0.966)**	**-0.082 (-0.156, -0.007)**

Source: Table 2.17, p50 of the submission, Table 2, p1216, Weitz 2017; Table 2 p704, Agnelli 2013, Table 4 p2509, Bauersachs 2010, Table 2, p1985 Brighton 2012, Table 2, p1965 Becattini 2012

Abbreviations: A2.5=.apixaban 2.5 mg; A5=apixaban 5 mg; ASA=aspirin; CI=confidence interval; ID=identification; n=number of participants, N=total participants in group; PBO=placebo; R10=rivaroxaban 10 mg; R20=rivaroxaban 20 mg

Notes: [1] recurrent VTE or VTE related death was a secondary efficacy outcome in Amplify EXT; [2] Reported as an HR in the submission.

Bold indicates a statistically significant difference

Comparative harms

6.11 The results for major bleeding are presented in Table 7. There were no statistically significant differences between the interventions (rivaroxaban 10 mg, rivaroxaban 20 mg, apixaban 2.5 mg), and their relevant comparators (aspirin, rivaroxaban 20 mg, placebo). The results of the comparison between aspirin and placebo for major bleeding in WARFASA and ASPIRE (used in ITC) also showed no statistically significant differences in the occurrence of bleeding events.

Table 7: Major bleeding comparison between trials

Trial ID	Intervention, n/N (%)	Comparators, n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)
Einstein CHOICE	R10 5/1127 (0.4)	R20 6/1107 (0.5)	0.81 (0.25, 2.70)[1] 0.819 (0.251, 2.674)	-0.001 (-0.007, 0.005)
		ASA 3/1131 (0.3)	1.64 (0.39, 6.84)[1] 1.673 (0.401, 6.982)	0.002 (-0.003, 0.007)
	R20 6/1107 (0.5)	ASA 3/1131 (0.3)	2.01 (0.50, 8.04)[1] 2.043 (0.512, 8.15)	0.003 (-0.002, 0.008)
Einstein EXT	R20 4/598 (6.0)	PBO 0/590	NA	0.007 (0, 0.013)
Amplify EXT	A2.5 2/840 (0.2)	A5 1/813 (0.1)	1.936 (0.176, 21.306)	0.001 (-0.003, 0.005)
		PBO 4/829 (0.5)	0.493 (0.091, 2.687)	-0.002 (-0.008, 0.003)
	A5 1/813 (0.1)	PBO 4/829 (0.5)	0.255 (0.029, 2.276)	-0.004 (-0.009, 0.002)
ASPIRE	ASA 8/411 (1.9)	PBO 6/411 (1.5)	1.333 (0.467, 3.809)	0.005 (-0.013, 0.023)
WARFASA	ASA 1/205 (0.5)	PBO 1/197 (0.5)	0.961 (0.061, 15.258)	0.000 (-0.014, 0.014)

Source: Table 2.18, p50-51 of the submission; Table 4 p1220 Weitz 2017, Table 2 p704 Agnelli 2013a; Table 4, p2509, Bauersachs 2010, Table 2, p1985 Brighton 2012, Table 2 p1965 Becattini 2012

Abbreviations: A2.5=apixaban 2.5 mg; A5= apixaban 5 mg; ASA=aspirin; CI=confidence interval; ID=identification; n=number of participants, N=total participants in group; PBO=placebo; R10=rivaroxaban 10 mg; R20= rivaroxaban 20 mg

Notes: [1] Reported as an HR in the submission.

Bold indicates a statistically significant difference

6.12 The results for clinically relevant non-major (CRNM) bleeding are presented in Table 8. There were no statistically significant differences in the risk of CRNM bleeding

between rivaroxaban 10 mg and aspirin or rivaroxaban 20 mg (Einstein CHOICE), between rivaroxaban 20 mg and aspirin (Einstein CHOICE), or between apixaban 2.5 mg and placebo (Amplify EXT). There was an increased risk of CRNM bleeds observed with rivaroxaban 20 mg compared with placebo (Einstein EXT), although this is tempered by some uncertainty as shown by the wide confidence intervals. There were no statistically significant differences between aspirin and placebo (ASPIRE, WARFASA) in the occurrence of CRNM bleeds.

Table 8: Major or CRNM bleeding comparison between trials

Trial ID	Intervention, n/N (%)	Comparators, n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)
Einstein CHOICE	R10 27/1127 (2.4)	R20 36/1107 (3.3)	0.73 (0.44-1.20) [1] 0.737 (0.45, 1.205)	-0.009 (-0.022, 0.005)
		ASA 23/1131 (2.0)	1.16 (0.67, 2.03) [1] 1.178 (0.680, 2.042)	0.004 (-0.009, 0.016)
	R20 36/1107 (3.3)	ASA 23/1131 (2.0)	1.59 (0.94, 2.69) [1] 1.599 (0.954, 2.681)	0.012 (-0.001, 0.025)
Einstein EXT	R20 32/598 (5.4)	PBO 7/590 (1.2)	**5.19 (2.3, 11.7) [1]** **4.51 (2.007, 10.137)**	**0.042 (0.022, 0.062)**
Amplify EXT	A2.5 27/840 (3.2)	A5 35/813 (4.3)	0.747 (0.456, 1.222)	-0.011 (-0.029, 0.007)
		PBO 22/829 (2.7)	1.211 (0.696, 2.109)	0.006 (-0.011, 0.022)
	A5 35/813 (4.3)	PBO 22/829 (2.7)	1.622 (0.96, 2.741)	0.017 (-0.001, 0.034)
ASPIRE	ASA 6/411 (1.5)	PBO 2/411 (0.5)	3 (0.609, 14.777)	0.01 (-0.004, 0.023)
WARFASA	ASA 3/205 (1.5)	PBO 3/197 (1.5)	0.961 (0.196, 4.704)	-0.001 (-0.024, 0.023)

Source: Table 2.19, p51 of the submission; Table 4 p1220 Weitz 2017, Table 2, p704 Agnelli 2013a Table 4 p2509, Bauersachs 2010, Table 2, p1985 Brighton 2012, Table 2, p1965 Becattine 2012

Abbreviations: A2.5=apixaban 2.5 mg; A5=apixaban 5 mg; ASA=aspirin; CI=confidence interval; ID=identification; n=number of participants, N=total participants in group; PBO=placebo; R10=rivaroxaban 10 mg; R20=rivaroxaban 20 mg

Note: [1] Reported as an HR in the submission.

Bold indicates a statistically significant difference

6.13 The rates of adverse events (AEs) and serious AEs (SEAs) emerging during treatment were similar across each treatment arm in Einstein CHOICE, Einstein EXT and Amplify EXT. The Amplify EXT reported three composite AE outcomes: any AE emerging during treatment; any serious AE emerging during treatment; and AEs resulting in permanent discontinuation of treatment. Overall, there were no differences noted across the studies in any of the safety outcomes reported.

6.14 A summary of key AEs is presented in Table 9, Table 10 and Table 11.

Table 9: Summary of any adverse events n (%)[1] in the randomised trials

Trial ID	Intervention	Comparator	RR (95% CI)	RD (95% CI)
Einstein CHOICE				
R10 (N=1127) vs R20 (N=1107)	R10 196 (17.4)	R20 194 (17.5)	0.992 (0.829, 1.188)	-0.001 (-0.033, 0.03)
R10 (N=1127) vs ASA (N=1131)	R10 196 (17.4)	ASA 193 (17.1)	1.019 (0.851, 1.221)	0.003 (-0.028, 0.034)
R20 (N=1107) vs ASA (N=1131)	R20 194 (17.5)	ASA 193 (17.1)	1.027 (0.857, 1.231)	0.005 (-0.027, 0.036)
Einstein EXT				
R20 (N=598) vs. PBO (N=590)	R20 349 (58.4)	PBO 337 (57.1)	1.021 (0.927, 1.126)	0.012 (-0.044, 0.069)
Amplify EXT				
A2.5 (N=840) vs. A.5 (N=811)	A2.5 596 (71.0)	A5 542 (66.8)	1.061 (0.994, 1.132)	0.041 (-0.003, 0.086)
A2.5 (N=840) vs. PBO (N=826)	A2.5 596 (71.0)	PBO 606 (73.4)	0.967(0.911, 1.026)	-0.024 (-0.067, 0.019)
A5 (N=811) vs. PBO (N=826)	A5 542 (66.8)	PBO 606 (73.4)	**0.91 (0.854, 0.97)**	**-0.065 (-0.11, -0.021)**

Source: Table 2.20 p53 of the submission, Table 4 p1220 Weitz 2017, Table 2, p704 Agnelli 2013a Table 4 p2509, Bauersachs 2010, Table

2, p1985 Brighton 2012, Table 2, p1965 Becattine 2012
Abbreviations: A2.5=apixaban 2.5 mg; A5=apixaban 5 mg; AE=adverse event; ASA=aspirin; CI=confidence interval; ID=identification; n=number; N=total participants in group; R10=rivaroxaban 10mg; R20=rivaroxaban 20 mg;
Notes: 1. Einstein CHOICE and Einstein EXT based on number of subjects. Amplify EXT based on any event emerging during treatment
Bold text indicates a statistically significant difference.

Table 10: Summary of any serious adverse events (SAE) n (%)[1] in the randomised trials

Trial ID	Intervention	Comparator	RR (95% CI)	RD (95% CI)
Einstein CHOICE				
R10 (N=1127) vs R20 (N=1107)	R10 94 (8.3)	R20 97 (8.8)	0.951 (0.725, 1.248)	-0.004 (-0.027, 0.019)
R10 (N=1127) vs. ASA (N=1131)	R10 94 (8.3)	ASA 99 (8.8)	0.952 (0.727, 1.248)	-0.004 (-0.027, 0.019)
R20 (N=1107) vs. ASA (N=1131)	R20 97 (8.8)	ASA 99 (8.8)	1.001 (0.766, 1.308)	-0.000 (-0.023, 0.024)
Einstein EXT				
R20 (N=598) vs. PBO (N=590)	R20 59 (9.9)	PBO 52 (8.8)	1.119 (0.784, 1.596)	0.011 (-0.023, 0.044)
Amplify EXT				
A2.5 (N=840) vs. A5 (N 811)	A2.5 112 (13.3)	A5 107 (13.2)	1.01 (0.789, 1.293)	0.001 (-0.031, 0.034)
A2.5 (N=840) vs PBO (N=826)	A2.5 112 (13.3)	PBO 158 (19.1)	**0.697 (0.558, 0.87)**	**-0.058 (-0.093, -0.023)**
A5 (N=811) vs. PBO (N=826)	A5 107 (13.2)	PBO 158 (19.1)	**0.689 (0.55, 0.864)**	**-0.059 (-0.095, -0.024)**
ASPIRE[2]				
ASA (N=411) vs PBO (N=411)	ASA 102 (24.8)	PBO 117 (28.5)	0.871 (0.694, 1.094)	-0.036 (-0.097, 0.024)

Source: Table 2.20 p53 of the submission, Table S1, Supplementary Appendix p8 Brighton 2012
Abbreviations: A2.5=apixaban 2.5 mg; A5=apixaban 5 mg; AE=adverse event; ASA=aspirin; CI=confidence interval; ID=identification n=number; N=total participants in group; R10=rivaroxaban 10mg; R20=rivaroxaban 20 mg; SAE=serious adverse event;
Notes: [1.] Einstein CHOICE and Einstein EXT based on number of subjects. Amplify EXT based on any serious event emerging during treatment; [2.] SAE leading to hospitalisation, Table 1 of Supplementary Appendix, Brighton 2012
Bold text indicates a statistically significant difference.

Table 11: Summary of adverse events (AE) resulting in death n (%)

Trial ID	Intervention	Comparator	RR (95% CI)	RD (95% CI)
Einstein CHOICE				
R10 (N=1127) vs. R20 (N=1107)	R10 3 (0.3)	R20 8 (0.7)	0.368 (0.097, 1.384)	-0.005 (-0.01, 0.001)
R10 (N=1127) vs. ASA (N=1131)	R10 3 (0.3)	ASA 4 (0.4)	0.752 (0.168, 3.355)	-0.001 (-0.005, 0.004)
R20 (N=1107) vs. ASA (N=1131)	R20 8 (0.7)	ASA 4 (0.4)	2.043 (0.617, 6.766)	0.004 (-0.002, 0.01)
Einstein EXT				
R20 (N=598) vs. PBO (N=590)	R20 1 (0.2)	PBO 2 (0.3)	0.0493 (0.044, 5.425)	-0.002 (-0.007, 0.004)

Source: Table 2.20 p53 of the submission
Abbreviations: A2.5=apixaban 2.5 mg; A5=apixaban 5 mg; AE=adverse event; ASA=aspirin; CI=confidence interval; ID=identification n=number; N=total participants in group; R10=rivaroxaban 10mg; R20=rivaroxaban 20 mg

6.15 The ITC was generated via a two-step process, using results from a meta-analysis reported by Robertson 2017 (which combined data from the WARFASA and ASPIRE studies) to generate intermediate indirect comparisons between either rivaroxaban 10 mg or apixaban 2.5 mg and the relevant common reference in the first instance, and the results from that intermediate comparison to inform the ITC of rivaroxaban 10 mg with apixaban 2.5 mg.

6.16 The results of the ITC for the primary efficacy and safety outcomes are presented in Table 12. For recurrent VTE or VTE-related deaths, methods 1A (using aspirin then placebo as the common reference) and 1B (using placebo then aspirin as the common reference) resulted in an identical indirect estimate of effect for rivaroxaban 10 mg vs. apixaban 2.5 mg, with an HR = 0.93 (95% CI: 0.39, 2.23; p=0.87). The submission concluded that since the estimate is very close to one and the p-value is greater than 0.05, it can be inferred that rivaroxaban 10 mg and apixaban 2.5 mg are equivalent.

This was reasonable.

6.17 The submission stated that the indirect estimate of effect of rivaroxaban 10 mg vs. apixaban 2.5 mg using methods 2A (using rivaroxaban 20 mg then placebo as the common reference) and 2B (using placebo then rivaroxaban 20 mg as the common reference) slightly favoured rivaroxaban 10 mg (HR=0.71, 95% CI: 0.22-2.27, p=0.56). However, the p-value was not significant, and the confidence interval overlapped the null value, thereby validating the results of methods 1A and 1B. Combined, these results indicate no statistically significant difference between rivaroxaban 10 mg and rivaroxaban 20 mg or apixaban 2.5 mg in the reduction of risk of recurrent VTE or VTE-related deaths. This was reasonable.

Table 12: Results from the two step ITC for key efficacy and safety outcomes

Trial or calculation	Comparison		Recurrent VTE or VTE-related death: RR (95% CI)	Major bleeding : RR (95% CI)	Major or CRNM bleeding : RR (95% CI)
Einstein CHOICE	R10 vs. ASA		**0.26 (0.14, 0.47)[5]** **0.26 (0.14, 0.48)**	1.64 (0.39, 6.84)[5] 1.67 (0.40, 6.98)	1.16 (0.67, 2.03)[5] 1.18 (0.68, 2.04)
	R10 vs. R20		0.75 (0.36, 1.54)[5] 0.75 (0.37, 1.54)	0.81 (0.25, 2.70)[5] 0.82 (0.25, 2.67)	0.73 (0.44, 1.20)[5] 0.74 (0.45, 1.21)
Amplify EXT	A2.5 vs PBO		**0.19 (0.11, 0.33)[5]** **0.19 (0.11, 0.33)**	0.49 (0.09, 2.64)[5] 0.49 (0.09, 2.69)	1.2 (0.69, 2.1)[5] 1.21 (0.70, 2.11)
Einstein EXT	R20 vs. PBO		**0.18 (0.09, 0.39)[5]** **0.19 (0.09, 0.40)**	NA	**5.19 (2.3, 11.7)[5]** **4.51 (2.01, 10.14)**
Robertson 2017	ASA vs. PBO		**0.68 (05, 0.92)[5]** **0.72 (0.56, 0.93)**	1.28 (0.47, 3.47)[5] 1.27 (0.48, 3.39)	1.48 (0.71, 3.06)[5] 1.78 (0.60, 5.27)
Intermediate indirect estimate of effect	R10 vs. PBO via ASA		**0.18 (0.09, 0.35)[5]** **0.19 (0.10, 0.35)**	2.10 (0.37, 12.04)[5] 2.08 (0.37, 11.79)	1.72 (0.69, 4.29)[5] 2.06 (0.61, 6.99)
	A2.5 vs. ASA via PBO		**0.28 (0.15, 0.52)[5]** **0.26 (0.15, 0.47)**	0.38 (0.05, 2.73)[5] 0.39 (0.05, 2.72)	0.81 (0.32, 2.03)[5] 0.67 (0.20, 2.29)
	A2.5 vs. R20 via PBO		**1.06 (0.42, 2.64)[5]** **1.06 (0.42, 2.64)**		**0.23 (0.09, 0.62)[5]** **0.23 (0.09, 0.62)**
	R10 vs. PBO via R20		**0.13 (0.38, 0.05)[5]** **0.13 (0.05, 0.38)**		**3.79 (1.46, 9.85)[5]** **3.79 (1.46, 9.85)**
Indirect estimate of effect	**R10 vs. A2.5**	**Method 1A[1]**	0.93 (0.39, 2.23) p=0.87[5] 0.99 (0.43, 2.28) p=0.97	4.28 (0.38, 48.66) p=0.24[5] 4.25 (0.38, 47.84) p=0.24	1.43 (0.49, 4.18) p=0.51[5] 1.72 (0.45, 6.58) p=0.43
		Method 1B[2]	0.93 (0.39, 2.23) p=0.87[5] 0.99 (0.43, 2.28) p=0.97	4.28 (0.38, 48.66) p=0.24[5] 4.25 (0.38, 47.84) p=0.24	1.43 (0.49, 1.48) p=0.51[5] 1.72 (0.45, 6.58) p=0.43
		Method 2A[3]	0.71 (0.22, 2.27) p=0.56[5] 0.71 (0.22, 2.27) p=0.56	-	**3.16 (1.05, 9.54) p=0.042[5]** **3.16 (1.05, 9.54) p=0.04**
		Method 2B[4]	0.71 (0.22, 2.27) p=0.56[5] 0.71 (0.22, 2.27) p=0.56	-	**3.16 (1.05, 9.54) p=0.042[5]** **3.16 (1.05, 9.54) p=0.04**

Source: Table 2.23, p61 of the submission; Table 2, p1216, Weitz 2017 Table 2 pg. 1216;, Table 2 p704, Agnelli 2013a Table 2 pg. 704, Table 4 p2509, Bauersachs 2010, Table 2, p 1985 Brighton 2012, Table 2, p 1965 Becattini 2012, Robertson 2017

Abbreviations: A2.5=apixaban 2.5 mg; ASA=aspirin; CI=Confidence Interval; PBO=placebo; RR=Risk Ratio; R10=rivaroxaban 10 mg; R20=rivaroxaban 20 mg

Notes: [1]. Two-step indirect of A2.5 vs. aspirin via placebo (Step 1) and then R10 vs. A2.5 via a-spirin (Step 2); [2]. Two-step indirect of R10 vs. placebo via aspirin (Step 1) and then R10 vs. A2.5 via placebo (Step 2);[3]. Two-step indirect of A2.5 vs. R20 via placebo (Step 1) and then R10 vs. A2.5 via R20 (Step 2); [4]. Two-step indirect of R10 vs. placebo via R20 (Step 1) and then R10 vs. A2.5 via placebo (Step 2); [5]. Reported as an HR in the submission;

Bold text indicates a statistically significant difference.

6.18 The results for major bleeding favoured apixaban 2.5 mg, (HR=4.28; 95%CI: 0.38, 48.66; p=0.24). The submission noted that the very large confidence intervals and non-significant p-value are indicative of a very small sample size and hence a large amount of uncertainty around this estimate. This was appropriate. Results for methods 2A and 2B were not available for this outcome given that a comparison for rivaroxaban 20 mg vs. placebo from Einstein EXT was not calculable due to no patients experiencing the outcome in the placebo group. This was reasonable.

6.19 The ITC was based on combining what the submission reported as RR from Amplify EXT, HR from Einstein CHOICE and Einstein EXT to the OR from Robertson et al. (2017; for ASPIRE and WARFASA) to create a composite HR metric. The ESC previously advised that such presentation of the results should be interpreted with caution given that HR should not be assumed to equal RR in the analysis and "that the incorrect assumption that HRs are equivalent to RRs undermines the indirect comparison" (Apixaban PSD, March 2015). During the evaluation, all the measures of association were re-expressed as RR. This did not alter the submission's conclusions with respect to the outcomes of the ITC.

Clinical claim

6.20 The submission described rivaroxaban 10 mg once daily in adults with a history of VTE for prevention of recurrent VTE as therapeutically equivalent to rivaroxaban 20 mg once daily in terms of the risk of VTE recurrence and VTE-related death whilst offering a slightly better safety profile in terms of major bleeding and CRNM bleeding. The claim was supported with respect to recurrent VTE or VTE-related death; there were no statistically significant differences in rates of major or CRNM bleeds.

6.21 The submission described rivaroxaban 10 mg as therapeutically equivalent to apixaban 2.5 mg twice daily when assessed on the risk of recurrent VTE and VTE-related death, major bleeding and CRNM bleeding. The results of the ITC of rivaroxaban 20 mg and apixaban 2.5 mg presented by the submission were consistent with the published literature and previous PBAC submission (Apixaban Public Summary Document March 2015) in which apixaban 2.5 mg was considered non-inferior to rivaroxaban 20 mg in terms of efficacy and safety.

6.22 The ESC noted that the claim of therapeutic equivalence was made on the basis of the direct and indirect treatment comparisons, although the direct comparison was not powered to demonstrate non-inferiority. Nevertheless, the ESC considered that the comparisons supported the claim of therapeutic equivalence in efficacy and with no additional risk of major or clinically relevant non-major bleeds.

6.23 The PBAC considered that the claim of therapeutic equivalence with respect to comparative effectiveness was reasonable.

6.24 The PBAC considered that the claim of therapeutical equivalence with respect to comparative safety was reasonable.

Economic analysis

6.25 The submission presented a cost-minimisation analysis for rivaroxaban 10 mg compared to rivaroxaban 20 mg and apixaban 2.5 mg. The submission assumed there was no difference in resource use between the drugs being compared other than the use of the drugs themselves. This was reasonable. The equi-effective doses used in the submission to inform the analysis were based on the dose relativity between rivaroxaban 10 mg once daily and rivaroxaban 20 mg once daily (Einstein CHOICE) and between rivaroxaban 10 mg once daily and apixaban 2.5 mg twice daily (ITC).

6.26 The submission presented a cost-minimising price for rivaroxaban 10 mg derived from the approved ex-manufacturer price (AEMP) and estimated cost per day of treatment for rivaroxaban 20 mg ($92.74). Pricing compared with apixaban 2.5 mg resulted in a slightly higher DPMQ of $93.06 due to the differences in the pack size. The requested price was based on the relativity between rivaroxaban 10 mg and rivaroxaban 20 mg; a request was not made for the higher price incorporating the relativity with apixaban 2.5 mg. This was appropriate.

6.27 The evaluation re-calculated the cost-minimising price for rivaroxaban 10 mg based on the effective AEMP for rivaroxaban 20 mg provided by the Department of Health (DoH). This resulted in an estimated effective DPMQ for rivaroxaban 10 mg of $[redacted].

6.28 In the PSCR, the sponsor noted that they were unable to validate the pricing information provided in the evaluation for the rivaroxaban effective ex-manufacturer price ([DVT]: 20 mg [28-pack] = $[redacted]). However, the sponsor also noted that "the effective DPMQ and AEMP for rivaroxaban 10mg will be finalised as part of a deed agreement with the pricing section post-PBAC recommendation." The Pre-PBAC Response clarified that the sponsor was seeking cost parity to the daily cost of rivaroxaban 20 mg [28 pack, DVT, PE, VTE].

Drug cost/patient/year

6.29 The average cost of rivaroxaban 10 mg per patient per 30-day pack was estimated by the submission to be $[redacted] based on the proposed listing price from the submission. This resulted in average dispensed cost of rivaroxaban per patient per year of $[redacted] ($[redacted]*365.25/30).

6.30 The average effective cost of rivaroxaban 10 mg per patient per 30-day pack was estimated in the evaluation to be $[redacted]. This resulted in average dispensed cost of rivaroxaban per patient per year of $[redacted]($[redacted]*365.25/30).

Estimated PBS usage & financial implications

6.31 This submission was not considered by DUSC. The submission presented a market share approach based on a 10% historical PBS sample on the use of rivaroxaban 20 mg and apixaban 2.5 mg. The submission assumed that the proposed listing would benefit the same pool of patients who are currently accessing the PBS-subsidised use of rivaroxaban 20 mg and apixaban 2.5 mg for the prevention of recurrent VTE without increasing the size of the eligible patient pool. Substitution would therefore occur for those two products in a split of [redacted]% for rivaroxaban 20 mg and [redacted]% for apixaban 2.5 mg. The submission also assumed an exponential growth in the treatment market. The use of the 10% PBS sample, market share approach, assumed proportion of substitution and market growth assumptions applied by the submission were reasonable.

6.32 The submission estimated that the requested listing resulted in a net increase of $[redacted] - $[redacted] per year over six years to the PBS (see Table 13).

Table 13: Estimated use and financial implications

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cost of rivaroxaban 10mg qd ($)						
without co-pay adjustments	[redacted]					
with co-pay adjustments	[redacted]					
with co-pay + rebate adjustments	[redacted]					
Cost offsets of substituted medications ($)						
without co-pay adjustments	[redacted]					
with co-pay adjustments	[redacted]					
with co-pay + rebate adjustments	[redacted]					
Net cost to PBS/RPBS ($)						
without co-pay adjustments	[redacted]					
with co-pay adjustments	[redacted]					
with co-pay + rebate adjustments	[redacted]					

Source: Table 4.13, p31 of the submission

Abbreviations: qd=quaque die (once a day), mg = milligram, PBS=Pharmaceutical Benefits Scheme, RPBS=Repatriation Pharmaceutical Benefits Scheme.

6.33 The evaluation revised the estimated financial implication by using effective prices. This resulted in a negligible change to the estimated net cost to the PBS/RPBS from that estimated in the submission (a net saving to PBS/RPBS of less than $10 million in Year 1 and increasing to a net saving of less than $10 million in Year 6).

6.34 There were some uncertainties associated with the estimation of the financial implications due to:

- The submission estimated that [redacted]% of patients initiating apixaban 2.5 mg between July 2015 and June 2017 switched from rivaroxaban 20 mg. The submission assumed that all of those patients would switch to rivaroxaban 10 mg if made available on the PBS, on the basis of a reduced treatment intensity. These

assumptions were unsubstantiated. This was likely to be an underestimate of the financial implication (as rivaroxaban 10 mg [redacted] apixaban 2.5 mg);

- The submission did not account for the possible substitution of rivaroxaban 10 mg for apixaban 2.5 mg in patients initiating treatment. This resulted in an overestimate of the financial impact (as apixaban 2.5 [redacted] rivaroxaban 10 mg).

These uncertainties are expected to have a negligible impact on the financial implications of listing rivaroxaban 10 mg.

6.35 At year 5, the estimated number of patients was 10,000 – 50,000 per year and the net cost to the PBS would be substantially less than $10 million per year.

Quality Use of Medicines

6.36 The submission noted that the proposed listing offers an additional, lower-intensity, treatment option in the prevention of recurrent VTE and thus some patients may opt for this treatment option in place of the two-comparator treatments. Appropriately, the submission did not attempt to quantify or claim any difference for these benefits.

7 PBAC Outcome

7.1 The PBAC recommended extending the listing of rivaroxaban 10 mg to include an Authority Required (STREAMLINED) listing for the prevention of recurrent venous thromboembolism (VTE). The PBAC considered that rivaroxaban 10 mg once daily was equivalent to rivaroxaban 20 mg once daily and equivalent to apixaban 2.5 mg twice daily in this indication.

7.2 The PBAC considered that rivaroxaban 10 mg will provide an appropriate lower strength alternative to rivaroxaban 20 mg in patients requiring ongoing VTE prophylaxis.

7.3 The PBAC considered the proposed main comparators, rivaroxaban 20 mg and apixaban 2.5 mg were appropriate, and that the PBS restriction for rivaroxaban 10 mg should align with that of the comparators.

7.4 The PBAC noted that the submission presented a direct comparison of rivaroxaban 10 mg with rivaroxaban 20 mg (Einstein CHOICE) and an indirect treatment comparison (ITC) of rivaroxaban 10 mg to apixaban 2.5 mg. The PBAC noted that while the submission did not present the details for the WARFASA and ASPIRE trials used to inform the ITC, this did not influence the interpretation of the results of the ITC nor the therapeutic conclusions.

7.5 The PBAC considered that rivaroxaban 10 mg was therapeutically equivalent to rivaroxaban 20 mg and apixaban 2.5 mg for the efficacy outcome of recurrent VTE or VTE-related death, and also had a similar safety profile, in terms of major bleeding and clinically relevant non-major bleeding. While the direct comparison was not powered

to demonstrate non-inferiority, the PBAC considered that the comparisons supported the claim of therapeutic equivalence in efficacy and with no additional risk of bleeds.

7.6 The PBAC noted that although the ITC results favoured apixaban 2.5 mg for major bleeding there was a large amount of uncertainty around this estimate. The PBAC recalled that the results of the ITC were consistent with those presented in the ITC of rivaroxaban 20 mg and apixaban 2.5 mg considered at the March 2015 PBAC meeting, in which the PBAC considered the medicines to be non-inferior.

7.7 The recommendation for listing rivaroxaban 10 mg once daily was on a cost-minimisation basis with rivaroxaban 20 mg once daily and apixaban 2.5 mg twice daily, at an equivalent cost per day.

7.8 The estimated utilisation assumed that substitution of use by the comparators would occur without an increase in the size of the eligible patient pool for these medicines. The PBAC noted the uncertainties around the estimates, however considered that the estimated utilisation was reasonable as the uncertainties were expected to have negligible impact.

7.9 The PBAC reaffirmed its March 2015 advice under Section 101(3BA) of the *National Health Act 1953* that rivaroxaban should be treated as interchangeable on an individual patient basis with apixaban.

7.10 The PBAC advised that rivaroxaban is suitable for prescribing by nurse practitioners within collaborative arrangements under a shared care model.

7.11 The PBAC recommended that the Early Supply Rule should apply.

7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
RIVAROXABAN 10 mg tablet, 30	1	5	Xarelto® Bayer Australia Limited

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Prevention of recurrent venous thromboembolism
PBS Indication:	Prevention of recurrent venous thromboembolism
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have a history of venous thromboembolism.
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. **Note** **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. Special Pricing Arrangements apply.

9 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.

10 Sponsor's Comment

Bayer welcomes the PBAC decision to recommend the PBS listing of Xarelto 10mg for the prevention of recurrent VTE.