

**6.01 APIXABAN
 filmed coated tablets, 2.5mg and 5mg;
 Eliquis®; Bristol-Myers Squibb.**

1 Purpose of Application

1.1 The submission sought an Authority Required listing for apixaban (Eliquis®) for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE).

2 Requested listing

2.1 The requested listing is outlined below, with the suggestions and additions proposed by the Secretariat added in italics and suggested deletions crossed out with strikethrough:

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|--|----------|-----------|------------------------------|-----------------------------------|
| APIXABAN apixaban 5 mg tablet, 28 | 28 | 0 | \$ [REDACTED] | Eliquis BQ |

| | |
|-----------------------------|--|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Deep vein thrombosis or pulmonary embolism |
| PBS Indication: | Deep vein thrombosis |
| Treatment phase: | Initial Treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | Patient must have confirmed acute symptomatic deep vein thrombosis or pulmonary embolism <i>AND</i> <i>Patient must not have symptomatic pulmonary embolism.</i> |

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|------------------------------|---|
| Administrative Advice | <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>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.</p> <p>Special Pricing Arrangements apply.</p> |
|------------------------------|---|

| | |
|------------------------------------|---|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Deep vein thrombosis or Pulmonary embolism |
| PBS Indication: | Pulmonary embolism |
| Treatment phase: | Initial Treatment |
| Restriction Level / Method: | Authority required (Streamlined) |
| Clinical criteria: | Patient must have confirmed acute symptomatic deep vein thrombosis or pulmonary embolism |
| Administrative Advice | <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>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.</p> <p>Special Pricing Arrangements apply.</p> |

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|--|----------|-------------|------------------------------|-----------------------------------|
| APIXABAN apixaban 5 mg tablet, 60 | 60 | 5 | \$ [REDACTED] | Eliquis BQ |

| | |
|---------------------------|--|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Deep vein thrombosis or pulmonary embolism |
| PBS Indication: | Deep vein thrombosis |
| Treatment phase: | Continuing Treatment |

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|-----------------------------|---|
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | <p>Patient must have confirmed acute symptomatic deep vein thrombosis or pulmonary embolism</p> <p>AND</p> <p><i>Patient must not have symptomatic pulmonary embolism.</i></p> |
| Administrative Advice | <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p>Note Shared Care Model: <i>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.</i></p> <p><i>Special Pricing Arrangements apply.</i></p> |

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|-----------------------------|---|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Deep vein thrombosis or Pulmonary embolism |
| PBS Indication: | Pulmonary embolism |
| Treatment phase: | Continuing Treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | <p>Patient must have confirmed acute symptomatic deep vein thrombosis or pulmonary embolism</p> |
| Administrative Advice | <p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p> <p>Note Shared Care Model: <i>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.</i></p> <p><i>Special Pricing Arrangements apply.</i></p> |

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| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|--|----------|-------------|------------------------------|-----------------------------------|
| APIXABAN apixaban 2.5 mg tablet, 60 | 60 | 5 | \$ [REDACTED] | Eliquis BQ |

| | |
|-----------------------------|--|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Prevention of recurrent venous thromboembolism |
| PBS Indication: | Prevention of recurrent venous thromboembolism |
| Treatment phase: | Continuing Treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | Patient must have confirmed a history of acute symptomatic deep vein venous thrombosis or pulmonary embolism <i>thromboembolism</i> AND <i>Patient must have undergone at least 6 months therapy with apixaban for the treatment of deep vein thrombosis; OR</i> <i>Patient must have undergone at least 6 months therapy with apixaban for the treatment of pulmonary embolism</i> |
| Administrative Advice | <i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised.</i> Note Shared Care Model: <i>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.</i> <i>Special Pricing Arrangements apply.</i> |

2.2 Listing was requested on a cost-minimisation basis compared to rivaroxaban.

3 Background

3.1 Apixaban was lodged under the TGA/PBAC parallel process. At the time of the PBAC meeting, a positive Delegates Overview was available.

3.2 Apixaban is currently listed on the PBS for prevention of stroke and systemic embolism in non-valvular atrial fibrillation in patients with one or more risk factors, and prevention of venous thromboembolic events in adult patients who have

undergone elective total hip or total knee replacement surgery. The PBAC has not previously considered apixaban for the requested restriction.

4 Clinical place for the proposed therapy

- 4.1 Venous thromboembolism (VTE) is the formation of blood clots in the venous system. VTE manifests as deep vein thrombosis (DVT) and/or pulmonary embolism (PE). VTE is usually treated with anticoagulants, medications that reduce the blood's ability to clot. Apixaban is a novel oral anticoagulant (NOAC), a new class of anticoagulants developed to allow administration with little requirement for monitoring and a better safety profile.
- 4.2 The proposed place in therapy of apixaban is as an alternative treatment option to rivaroxaban, which is currently the only PBS-listed NOAC in this patient population.

5 Comparator

- 5.1 The submission nominated rivaroxaban as the main comparator. The main argument provided in support of this nomination is that rivaroxaban is currently the only NOAC listed for the indication sought. The sponsor also nominated dabigatran as the supplementary comparator. However, dabigatran is not TGA registered or PBS listed for the treatment or secondary prevention of DVT and PE. The evaluation considered that rivaroxaban is an appropriate comparator.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no 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 an indirect comparison of apixaban and rivaroxaban:

For acute treatment of VTE using enoxaparin/warfarin as the common comparator, apixaban 5mg twice daily (AMPLIFY) vs. rivaroxaban 20mg daily (EINSTEIN-DVT, EINSTEIN-PE).

For extended treatment of VTE using placebo as the common comparator, apixaban 2.5mg or 5mg twice daily (AMPLIFY-EXT) vs. rivaroxaban 20mg daily (EINSTEIN-EXT).

- 6.4 Details of the trials presented in the submission were provided in the table below.

Trials and associated reports presented in the submission

| Trial ID | Protocol title/ Publication title | Publication citation |
|---------------------------|--|--|
| Apixaban trials | | |
| AMPLIFY | Clinical Study Report: CV185056 (B0661001). Agnelli G, Buller H, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI. Oral apixaban for the treatment of acute venous thromboembolism. Botticelli Investigators, Writing Committee, Buller H, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. | Date of report: 13 March 2014. <i>N Engl J Med</i> 2013; 369: 799-808. <i>Journal of Thrombosis & Haemostasis</i> 2008; 6(8):1313-8. |
| AMPLIFY-EXT | Clinical Trial Report: CV185057 (B0661002). Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI, AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. | Date of report: 13 March 2014. <i>N Engl J Med</i> 2013; 368(8):699-708. |
| Rivaroxaban trials | | |
| EINSTEIN-DVT/EXT | EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovello F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. Wang Y, Wang C, Chen Z, Zhang J, Liu Z, Jin B, Ying K, Liu C, Shao Y, Jing Z, Meng IL, Prins MH, Pap AF, Muller K, Lensing AW, Chinese EINSTEIN Investigators. Rivaroxaban for the treatment of symptomatic deep-vein thrombosis and pulmonary embolism in Chinese patients: a subgroup analysis of the EINSTEIN DVT and PE studies. Prins MH, Lensing AW, Bauersachs R, van Bellen B, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Raskob GE, Berkowitz SD, Wells PS, EINSTEIN Investigators. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Bamber L, Wang MY, Prins MH, Ciniglio C, Bauersachs R, Lensing AW, Cano SJ. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic deep-vein thrombosis. Buller HR, Lensing AW, Prins MH, Agnelli G, Cohen A, Gallus AS, Misselwitz F, Raskob G, Schellong S, Segers A Einstein-DVT Dose-Ranging Study investigators. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. | <i>N Engl J Med</i> 2010; 363(26):2499-510. <i>Thrombosis Journal</i> 2013; 11(1):25. <i>Thrombosis Journal</i> 2013; 11(1):21. <i>Thrombosis and Haemostasis</i> 2013 110(4):732-41 <i>Blood</i> 2008; 112(6):2242-7. |
| EINSTEIN-PE | EINSTEIN-PE Investigators, Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. | <i>N Engl J Med</i> 2012; 366(14):1287-97. |

Source: Table 3 (pB.12) of the submission, relevant references and individual clinical study reports.

6.5 The key features of the trial included in the indirect analysis are summarised in the table below.

Key features of the included evidence – indirect comparison

| Trial | N | Design/duration | Risk of bias | Patient population | Primary Outcome |
|--|-------|---|--------------|---------------------------------|--|
| Apixaban vs. enoxaparin/warfarin | | | | | |
| AMPLIFY | 5,395 | DB, R, MC. Non-inferiority. 6 months. | Low | Symptomatic proximal DVTs only. | Adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or VTE-related death |
| Apixaban vs. placebo | | | | | |
| AMPLIFY-EXT | 2,482 | DB, R, MC. Superiority. 12 months. | Low | Symptomatic proximal DVTs only. | Adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death. |
| Rivaroxaban vs. enoxaparin/warfarin | | | | | |
| EINSTEIN-DVT | 3449 | R, MC, OL. Non-inferiority. 3, 6, or 12 months. | Unclear | Symptomatic proximal DVTs only. | Recurrent VTE (composite of DVT or nonfatal or fatal PE). |
| EINSTEIN-PE | 4,832 | R, MC, OL. Non-inferiority. 3, 6, or 12 months. | Unclear | Symptomatic PE. | Symptomatic recurrent VTE (composite of fatal or nonfatal PE or DVT). |
| Rivaroxaban vs. placebo | | | | | |
| EINSTEIN-EXT | 1196 | R, MC, OL. Superiority. 6 or 12 months. | Unclear | Patients from EINSTEIN trials | Recurrent VTE (composite of DVT or nonfatal or fatal PE). |

Source: Table 3 (pB.12) of the submission, individual trial reports and publications

Abbreviations: DB, double blind; DVT, deep-vein thrombosis; MC, multi-centre; OL, open label; PE, pulmonary embolism; R, randomised; VTE, venous thromboembolism

- 6.6 The ESC noted that there were some differences across trials in baseline patient characteristics, however considered that there was no clear direction of bias.

Comparative effectiveness

- 6.7 For the acute treatment of VTE, the submission proposed the non-inferiority margins used in the AMPLIFY trial (to determine non-inferiority of apixaban to warfarin) be used in the indirect comparison of apixaban versus rivaroxaban (i.e. upper limit of the 95% confidence interval less than 1.8 for the relative risk and less than 3.5% for the risk difference).
- 6.8 No non-inferiority margin was nominated for extended treatment of VTE. The submission stated that non-inferiority would have to be determined by considering how close the upper limits of 95% CIs for RR are to 1, which would involve some degree of subjectivity and clinical judgement. However, the ESC considered that a pre-specified clinically meaningful non-inferiority margin with appropriate clinical justification is still necessary to appropriately test the hypothesis of similar efficacy.

Acute treatment of venous thromboembolism

Results of recurrent VTE or VTE-related death for the acute treatment of VTE

| Trial ID | Apixaban 5mg n/N (%) | Warfarin n/N (%) | Rivaroxaban 20mg n/N (%) | Risk Difference RD (95% CI) | Relative Risk RR/HR (95% CI) |
|--|-------------------------|---------------------|--------------------------------|--------------------------------|---------------------------------|
| Apixaban | | | | | |
| AMPLIFY | 59/2609 (2.26%) | 71/2635 (2.69%) | - | -0.43% (-1.27, 0.41) | 0.84 (0.60, 1.18) |
| Rivaroxaban | | | | | |
| EINSTEIN-DVT | - | 51/1718 (2.97%) | 36/1731 (2.08%) | -0.89% (-1.94, 0.16) | 0.70 (0.46, 1.07) |
| EINSTEIN-PE | - | 44/2413 (1.82%) | 50/2419 (2.07%) | 0.24% (-0.54, 1.02) | 1.13 (0.76, 1.69) |
| Meta-analysis (I ² =66% for RD; 62% for RR) | | | | -0.27% (-1.38, 0.85) | 0.90 (0.56, 1.43) |
| Indirect comparison apixaban vs. rivaroxaban | | | | -0.17% (-1.56, 1.23) | 0.94 (0.52, 1.68) |

Source: Table 32 (pB.79) of the submission

Abbreviations: HR, hazard ratio; NR, not reported; RR, relative risk; VTE, venous thromboembolism

Note: AMPLIFY reported relative risk, while EINSTEIN-DVT and EINSTEIN-PE reported hazards ratios.

- 6.9 In the indirect comparison of acute treatment of VTE, apixaban was non-inferior to rivaroxaban, with the upper confidence limit (1.68) less than the nominated non-inferiority margin of 1.8 and the upper confidence limit of the risk difference (1.23%) less than the nominated non-inferiority margin of 3.5%.

Extended treatment of venous thromboembolism

Results of recurrent VTE or VTE-related death for the extended treatment of VTE

| Trial ID | Apixaban n/N (%) | Placebo n/N (%) | Rivaroxaban 20mg n/N (%) | Risk Difference RD (95% CI) | Relative Risk RR/HR (95% CI) |
|--|---------------------|--------------------|--------------------------------|--------------------------------|---------------------------------|
| Apixaban | | | | | |
| AMPLIFY-EXT, Apixaban 2.5mg | 14/840 (1.67%) | 73/829 (8.81%) | - | -7.14% (-9.25, -5.02) | 0.19 (0.11, 0.33) |
| AMPLIFY-EXT, Apixaban 5mg | 14/813 (1.72%) | 73/829 (8.81%) | - | -7.08% (-9.21, -4.96) | 0.20 (0.11, 0.34) |
| Rivaroxaban | | | | | |
| EINSTEIN-EXT | - | 42/594 (7.07%) | 8/602 (1.33%) | -5.74% (-8.00, -3.49) | 0.19 (0.09, 0.40) |
| Indirect comparison apixaban 2.5mg vs. rivaroxaban | | | | -1.40% (-4.49, 1.69) | 1.01 (0.40, 2.57) |
| Indirect comparison apixaban 5mg vs. rivaroxaban | | | | -1.34% (-4.44, 1.76) | 1.04 (0.41, 2.65) |

Source: Table 33 (pB.80) of the submission

Abbreviation: HR, hazard ratio; RR, relative risk; VTE, venous thromboembolism

Note: AMPLIFY-EXT reported relative risk while EINSTEIN-EXT reported hazard ratio

In the indirect comparison for extended treatment of VTE, there was no statistically significant difference between apixaban 2.5mg and 5mg compared to rivaroxaban in recurrent VTE or VTE-related death. No non-inferiority margin was identified for this analysis. The confidence intervals are wide and the evaluation considered that it was not possible to conclude non-inferiority between apixaban and rivaroxaban.

- 6.10 The indirect comparison was based on combining RRs from AMPLIFY to the HRs estimates from EINSTEIN to create a composite hazard/risk metric. These results should be interpreted with caution given that hazard ratios were incorrectly assumed to equal relative risk in the analyses. A hazard ratio is a ratio of hazard rates where the probability that any given trial subject, having survived to time t, experiences a

trial endpoint at time t in the treatment arm divided by the same quantity in the comparator arm. By contrast a relative risk is not a ratio of rates but a ratio of risk, where the proportion of endpoint events that occurred during the observation period in the treatment arm compared to the same in the comparator. The former is explicitly a metric that is calculated “in-trial” or within the observation period and is unit less with regards to time, the latter is only calculable at the end of observation period and is expressed in terms of average or median trial duration. HRs capture the rate at which a trial subject in the treatment arm may progress or experience the trial endpoint slower relative to the comparator arm, but they do not quantify how much slower in units of time. The ESC considered that the incorrect assumption that HRs are equivalent to RRs undermines the indirect comparison which attempts to fuse RRs from the AMPLIFY trial to the HRs estimated in the EINSTEIN-DVT/PE trial. The Pre-Sub-Committee Response (PSCR) (p1-2) reiterated that HRs are equal to RR and provide a citation with the qualification that they may approximate each other in circumstances where the endpoint is rare. The ESC considered that whilst this may be true under the rare event assumption, it is not always the case (i.e. an endpoint may be rare, however the RRs still do not approximate the HRs).

- 6.11 The PSCR (p5) presented a sensitivity analysis using both adjusted and unadjusted methods. The results are shown in the table below.

Comparison - apixaban vs rivaroxaban via warfarin (as acute treatment) on recurrent VTE or VTE related death

| Direct comparison Apixaban and rivaroxaban as acute therapy via warfarin on Recurrent VTE or VTE related death | | | | | | | | |
|--|---|----------------|---------------------------|----------------------|--------------------------------------|--------------------------------|---------------------------|-----|
| Study: Comparison | Treatment | | Warfarin | | Adjusted HR ¹ (95% CI) | Unadjusted comparison (95% CI) | | |
| | Popn N | Event n (%) | Popn N | Event n (%) | | RR | RD | NNT |
| AMPLIFY: Apix 5mg BD vs Warf | 2609 | 59 (2.26%) | 2635 | 71 (2.69%) | 0.84 (0.6, 1.18) | 0.839 (0.597, 1.180) | -0.43% (-1.27%, 0.41%) | NA |
| EINSTEIN-DVT: Riva 20mg OD vs Warf | 1731 | 36 (2.08%) | 1718 | 51 (2.97%) | 0.68 (0.44, 1.04) | 0.701 (0.460, 1.068) | -0.89% (-1.94%, 0.16%) | NA |
| EINSTEIN-PE: Riva 20mg OD vs Warf | 2419 | 50 (2.07%) | 2413 | 44 (1.82%) | 1.12 (0.75, 1.68) | 1.134 (0.759, 1.693) | 0.24% (-0.54%, 1.02%) | NA |
| Meta-analysed EINSTEIN- DVT+PE: Riva 20mg OD vs Warf | 4150 | 86 (2.07%) | 4131 | 95 (2.30%) | 0.878 (0.538, 1.431) | 0.895 (0.559, 1.434) | -0.27% (-1.38%, 0.85%) | NA |
| ¹ In AMPLIFY, adjusted relative risk (RR) was estimated; in other studies, hazard ratio (HR) was estimated. | | | | | | | | |
| Indirect comparison Apixaban v rivaroxaban as acute therapy via warfarin on Recurrent VTE or VTE related death | | | | | | | | |
| Treatments | Comparison | | Indirect estimate (95%CI) | | | | | |
| | Studies | | Adjusted HR ¹ | Unadjusted RR | Unadjusted RD | | | |
| Apix 5mg BD vs Riva 20mg OD | AMPLIFY vs Meta-analysed EINSTEIN- DVT+PE | | 0.957 (0.528, 1.735) | 0.938 (0.524, 1.678) | -0.17% (-1.56%, 1.23%) | | | |
| ¹ In AMPLIFY, adjusted relative risk (RR) was estimated; in other studies, hazard ratio (HR) was estimated. | | | | | | | | |

Abbreviations: Apix, apixaban; Riva, rivaroxaban; Pbo, placebo; N, study population; n, number of patients with event; Popn, population
Source: PSCR p5

The ESC noted that the sensitivity analysis demonstrated a similar set of results.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Comparative harms

6.12 Safety outcomes reported were major bleeding (primary safety outcome in AMPLIFY, AMPLIFY-EXT, EINSTEIN-EXT), first major or clinically relevant non-major (CRNM) bleeding (primary safety outcome in EINSTEIN-DVT, EINSTEIN-PE), or both (RE-SONATE, RE-COVER & RE-COVER I). The ESC considered that there was no clear safety advantage over rivaroxaban, but noted that the submission proposed a cost-minimisation approach. The results are summarised in the tables below.

Summary of comparative harms in acute therapy, apixaban versus rivaroxaban

| | Apixaban n/N | Warfarin n/N | Riva n/N | RR (95% CI) | Event rate/100 patients | | | RD (95% CI) |
|---|-----------------|-----------------|-------------|----------------------|-------------------------|----------|-------|--------------------------|
| | | | | | Apixaban | Warfarin | Riva | |
| Harms (acute therapy) | | | | | | | | |
| Major bleed | | | | | | | | |
| Apixaban 5mg | | | | | | | | |
| AMPLIFY | 15/2676 | 49/2689 | - | 0.31 (0.17, 0.55) | 0.56 | 1.82 | - | -1.26% (-1.84, -0.68) |
| Rivaroxaban 20mg | | | | | | | | |
| EINSTEIN-DVT | - | 20/1711 | 14/1718 | 0.70 (0.35, 1.38) | - | 1.17 | 0.81 | -0.35% (-1.02, 0.31) |
| EINSTEIN-PE | - | 52/2405 | 26/2412 | 0.50 (0.31, 0.80) | - | 2.16 | 1.08 | -1.08% (-1.80, -0.37) |
| Meta-analysis | | 72/4116 | 40/4130 | 0.56 (0.38, 0.82) | - | 1.75 | 0.97 | -0.71% (-1.44, 0.03) |
| Indirect comparison: apixaban 5mg vs. rivaroxaban 20mg | | | | 0.55 (0.28, 1.11) | - | | | -0.55% (-1.49, 0.38) |
| Major or CRNM bleeding | | | | | | | | |
| Apixaban 5mg | | | | | | | | |
| AMPLIFY | 115/2676 | 261/2689 | - | 0.44 (0.36, 0.55) | 4.30 | 9.71 | - | -5.41% (-6.77, -4.05) |
| Rivaroxaban 20mg | | | | | | | | |
| EINSTEIN-DVT | - | 138/1711 | 139/1718 | 1.00 (0.80, 1.26) | - | 8.07 | 8.09 | 0.03% (-1.80, 1.85) |
| EINSTEIN-PE | - | 274/2405 | 249/2412 | 0.91 (0.77, 1.07) | - | 11.39 | 10.32 | -1.07% (-2.83, 0.69) |
| Meta-analysis | | 412/4116 | 388/4130 | 0.94 (0.82, 1.07) | - | 10.00 | 9.39 | -0.54% (-1.81, 0.72) |
| Indirect comparison: apixaban 5mg vs. rivaroxaban 20mg | | | | 0.47 (0.37, 0.61) | - | | | -4.87% (-6.72, -3.01) |

Abbreviations: CRNM, clinically relevant non-major; NE, not estimated; Riva, rivaroxaban; RD, risk difference; RR, risk ratio.

Source: Table 36, p B.84 of the submission.

Note: AMPLIFY reported relative risk, while EINSTEIN-DVT and EINSTEIN-PE reported hazards ratios.

Summary of harms in extended therapy, apixaban versus rivaroxaban

| Benefits (extended therapy) | | | | | | | | |
|---|-----------------|----------------|-------------|------------------------|-------------------------|---------|------|----------------------------|
| | Apixaban n/N | Placebo n/N | Riva n/N | RR (95% CI) | Event rate/100 patients | | | RD (95% CI) |
| | | | | | Apixaban | Placebo | Riva | |
| Harms (extended therapy) | | | | | | | | |
| Major bleed | | | | | | | | |
| Apixaban 2.5mg | | | | | | | | |
| AMPLIFY-EXT | 2/840 | 4/826 | - | 0.49 (0.09, 2.67) | 0.24 | 0.48 | - | -0.25% (-0.82, 0.33) |
| Apixaban 5mg | | | | | | | | |
| AMPLIFY-EXT | 1/811 | 4/826 | - | 0.26 (0.03, 2.27) | 0.12 | 0.48 | - | -0.36% (-0.89, 0.17) |
| Rivaroxaban 20mg | | | | | | | | |
| EINSTEIN-EXT: | - | 0/590 | 4/598 | 8.88 (0.48, 164.57) | - | 0 | 0.67 | 0.67% (-0.06, 1.40) |
| Indirect comparison: apixaban 2.5mg vs. rivaroxaban 20mg | | | | 0.06 (0.00, 1.62) | - | | | -0.92% (-1.85%, 0.02%) |
| Indirect comparison: apixaban 5mg vs. rivaroxaban 20mg | | | | 0.03 (0.00, 1.10) | - | | | -1.03% (-1.93%, -0.13%) |
| Major or CRNM bleed | | | | | | | | |
| Apixaban 2.5mg | | | | | | | | |
| AMPLIFY-EXT | 27/840 | 22/826 | - | 1.21 (0.69, 2.10) | 3.21 | 2.66 | - | 0.55% (-1.07, 2.17) |
| Apixaban 5mg | | | | | | | | |
| AMPLIFY-EXT | 35/811 | 22/826 | - | 1.62 (0.96, 2.74) | 4.32 | 2.66 | - | 1.65% (-0.13, 3.43) |
| Rivaroxaban 20mg | | | | | | | | |
| EINSTEIN-EXT: | - | 7/590 | 36/598 | 5.07 (2.28, 11.31) | - | 1.19 | 6.02 | 4.82% (2.74, 6.93) |
| Indirect comparison: apixaban 2.5mg vs. rivaroxaban 20mg | | | | 0.24 (0.09, 0.63) | - | | | -4.28% (-6.93%, -1.63%) |
| Indirect comparison: apixaban 5mg vs. rivaroxaban 20mg | | | | 0.32 (0.12, 0.83) | - | | | -3.18% (-5.93%, -0.43%) |

Abbreviations: CRNM, clinically relevant non-major; NE, not estimated; PBO, placebo; RD, risk difference; Riva, rivaroxaban; RR, risk ratio.

Source: Table 37, p B.85 of the submission.

Note: AMPLIFY-EXT reported relative risk while EINSTEIN-EXT reported hazard ratio

Clinical claim

- 6.13 The submission claimed apixaban is non-inferior to the main comparator rivaroxaban in terms of efficacy and is superior to rivaroxaban with regard to major/clinically relevant non-major bleeding. The evaluation considered that the claim is adequately supported for acute treatment (up to 6 months) but not for extended treatment of VTE. Although this result should be interpreted with caution given the incorrect assumption the RRs are equivalent to HRs, the ESC noted that the PSCR (p5) presented a sensitivity analysis repeating the comparison with unadjusted RRs from all trials, rather than the composite HR/RR metric of the primary analysis. The ESC noted that the sensitivity analysis found similar results.
- 6.14 The submission claimed apixaban is non-inferior to the supplementary comparator dabigatran for the efficacy outcome, and is superior to dabigatran with regard to major or clinically relevant non-major bleeding. The evaluation considered that the

claim was adequately supported for acute treatment (up to 6 months) but not for extended treatment of VTE.

- 6.15 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.16 The PBAC considered that the data supported a conclusion of non-inferior comparative safety.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

- 6.17 The submission presented a cost minimisation analysis based on the non-inferiority of apixaban (2.5mg and 5mg twice daily regimens) to rivaroxaban (20mg daily) and equi-effective treatment regimens including initial titration and continuing treatment over the first 180 days of therapy. This approach was previously accepted by the PBAC in the rivaroxaban March 2013 submission and was reasonable. Current rivaroxaban and apixaban PBS listings are subject to special pricing arrangements, and the requested effective price of apixaban was not presented.
- 6.18 Extended treatment was not included in the analysis. The requested apixaban price for extended therapy was derived from currently listed rivaroxaban and apixaban items adjusted for 28 day versus 30 day script durations.

Estimated PBS usage & financial implications

- 6.19 The submission presented a combined epidemiological and market share approach to estimate utilisation and the financial implications associated with the listing of apixaban.

Estimated use and financial implications

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|--|--------|--------|--------|--------|--------|
| Estimated extent of use: initial treatment titration | | | | | |
| No. treated with apixaban | | | | | |
| Market share | % | % | % | % | % |
| Scripts ^a | | | | | |
| Cost of apixaban (less copay) | \$ | \$ | \$ | \$ | \$ |
| Estimated extent of use: continuing acute treatment (to 6 months) | | | | | |
| No. treated with apixaban | | | | | |
| Market share | % | % | % | % | % |
| Scripts ^b | | | | | |
| Cost of apixaban (less copay) | \$ | \$ | \$ | \$ | \$ |
| Estimated extent of use: extended treatment (6 to 12 months) | | | | | |
| No. treated with apixaban | | | | | |
| Market share | % | % | % | % | % |
| Scripts ^b | | | | | |
| Cost of apixaban (less copay) | \$ | \$ | \$ | \$ | \$ |
| Estimated net cost to PBS | | | | | |
| Cost of apixaban | \$ | \$ | \$ | \$ | \$ |
| Savings from substituted rivaroxaban | \$ | \$ | \$ | \$ | \$ |
| Net cost to the PBS | \$ | \$ | \$ | \$ | \$ |

^a 1 script per patient.

^b assuming 85% compliance and 4 scripts per patient

Source: Table 5 (pE.12), Table 13 (pE.18) of the submission; Excel spreadsheet "Eliquis Section E_final.xlsx", attached to the submission

- 6.20 The submission estimated that at year 5, the number of scripts would be 10,000 – 50,000 per year and the net cost to the PBS/RPBS would be a saving of less than \$10 million per year.
- 6.21 Rivaroxaban is subject to a special pricing arrangement. The evaluation considered that the market uptake rates, based on the assumption that rivaroxaban will continue to dominate the market, are low and may be underestimated. The ESC noted that the financial impact may be underestimated through use of incorrect assumptions regarding 'compliance' and 'persistence' as the reported rates were too low. However, the ESC did not consider this to be a major issue, as it was expected that substitution patterns would result in budget neutrality.

Quality Use of Medicines

- 6.22 The submission addressed quality use of medicines issues. A proposal presented in the submission proposed to improve patient adherence and education of health care professionals.

Financial Management – Risk Sharing Arrangements

- 6.23 The submission provided no details of risk sharing arrangements. The sponsor acknowledged that a financial management (or risk sharing) arrangement is likely to be required as a condition of listing, consistent with the current special pricing arrangements for rivaroxaban in VTE treatment and apixaban 5mg in atrial fibrillation.

- 6.24 The PBAC considered that apixaban may take a larger market share than rivaroxaban for the treatment of VTE. The PBAC recommended that apixaban should join the same risk sharing arrangement as rivaroxaban, for the same PBS indications, as this would mitigate any risk of additional costs to the Commonwealth.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of apixaban for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) on a cost-minimisation basis with rivaroxaban. The equi-effective doses are apixaban 2.5mg and 5mg twice daily to rivaroxaban 20 mg daily.
- 7.2 The PBAC considered that the apixaban restrictions should have the same criteria and conditions as rivaroxaban for VTE.
- 7.3 The PBAC accepted rivaroxaban as an appropriate comparator.
- 7.4 The PBAC noted the limitations of the indirect comparisons as outlined in Paragraphs 6.7 to 6.16 above, including that the analyses assumed that hazard ratios may be used as relative risks, and also the wide confidence intervals and lack of a clinically meaningful non-inferiority margin for the indirect comparison in the extended treatment of VTE patient population. However, the PBAC concluded that apixaban is non-inferior to rivaroxaban in terms of efficacy and safety. In forming this view the PBAC considered, in addition to the evidence presented, the totality of the comparative evidence that it had seen for apixaban, including that seen for the atrial fibrillation indication.
- 7.5 The PBAC considered that apixaban is suitable for prescribing by nurse practitioners within collaborative arrangements under a shared care model.
- 7.6 The PBAC recommended that the Safety Net 20 Day Rule should apply to the continuing treatment as it applies to other long-term oral prophylactic antithrombotic agents.
- 7.7 Advice to the Minister under subsection 101(3BA) of the Act
In accordance with subsection 101(3BA) of the Act the PBAC advised that it is of the opinion that apixaban should be treated as interchangeable on an individual patient basis with rivaroxaban.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

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| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Proprietary Name and Manufacturer | |
|--|----------|-------------|-----------------------------------|----|
| APIXABAN apixaban 5 mg tablet, 28 | 28 | 0 | Eliquis | BQ |

| | |
|-----------------------------|--|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Deep vein thrombosis |
| PBS Indication: | Deep vein thrombosis |
| Treatment phase: | Initial Treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | Patient must have confirmed acute symptomatic deep vein thrombosis AND Patient must not have symptomatic pulmonary embolism. |
| Administrative Advice | <i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised.</i> Note Shared Care Model: <i>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.</i> <i>Special Pricing Arrangements apply.</i> |

| | |
|-----------------------------|--|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Pulmonary embolism |
| PBS Indication: | Pulmonary embolism |
| Treatment phase: | Initial Treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | Patient must have confirmed acute pulmonary embolism |

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| | |
|------------------------------|---|
| Administrative Advice | <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>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.</p> <p>Special Pricing Arrangements apply.</p> |
|------------------------------|---|

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|--|----------|-------------|------------------------------|-----------------------------------|
| APIXABAN apixaban 5 mg tablet, 60 | 60 | 5 | | Eliquis BQ |

| | |
|------------------------------------|---|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Deep vein thrombosis |
| PBS Indication: | Deep vein thrombosis |
| Treatment phase: | Continuing Treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | Patient must have confirmed acute symptomatic deep vein thrombosis AND Patient must not have symptomatic pulmonary embolism. |
| Administrative Advice | <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>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.</p> <p>Special Pricing Arrangements apply.</p> |

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| | |
|-----------------------------|--|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Pulmonary embolism |
| PBS Indication: | Pulmonary embolism |
| Treatment phase: | Continuing Treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | Patient must have confirmed acute symptomatic pulmonary embolism |
| Administrative Advice | <i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised.</i> Note Shared Care Model: <i>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.</i> <i>Special Pricing Arrangements apply.</i> |

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|--|----------|-----------|------------------------------|-----------------------------------|
| APIXABAN apixaban 2.5 mg tablet, 60 | 60 | 5 | | Eliquis BQ |

| | |
|-----------------------------|--|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Prevention of recurrent venous thromboembolism |
| PBS Indication: | Prevention of recurrent venous thromboembolism |
| Treatment phase: | Continuing Treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | Patient must have a history of venous thromboembolism |

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| | |
|-----------------------|---|
| Administrative Advice | <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>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.</p> <p>Special Pricing Arrangements apply.</p> |
|-----------------------|---|

| | |
|-----------------------------|---|
| Category / Program | GENERAL – General Schedule (Code GE) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Pulmonary embolism |
| PBS Indication: | Pulmonary embolism |
| Treatment phase: | Continuing Treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | Patient must have confirmed acute symptomatic pulmonary embolism |
| Administrative Advice | <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>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.</p> <p>Special Pricing Arrangements apply.</p> |

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

The Sponsor welcomes the recommendation to make apixaban available on the PBS for treatment of patients with VTE.