

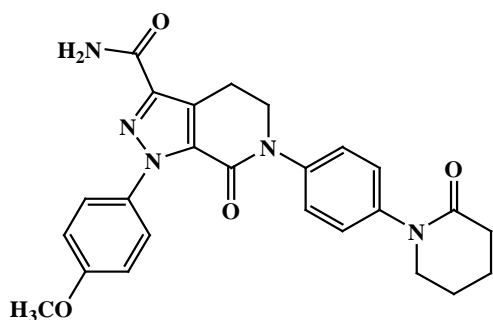
PRODUCT INFORMATION

ELIQUIS[®]

Apixaban

NAME OF THE MEDICINE

Apixaban, a selective inhibitor of the coagulation Factor Xa (FXa), is chemically described as 1-(4-Methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide. Its molecular formula is C₂₅H₂₅N₅O₄, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



CAS Number: 503612-47-3

DESCRIPTION

Apixaban is a white to pale yellow powder. At physiological pH (1.2 - 6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL. The octanol/water partition coefficient is 44.7 at pH 7.4.

ELIQUIS film-coated tablets are available for oral administration in strengths of 2.5 mg and 5 mg apixaban with the following inactive ingredients: anhydrous lactose, cellulose - microcrystalline, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, glycerol triacetate and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

PHARMACOLOGY

Pharmacodynamics

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (FXa inhibition). As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. They are not recommended to assess the pharmacodynamic effects of apixaban.

Apixaban also demonstrates anti-FXa activity as evident by reduction in FXa enzyme activity in the Rotachrom[®] Heparin chromogenic assay. Anti-FXa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching maximum values at the time

of apixaban peak plasma concentrations. The relationship between apixaban plasma concentration and anti-FXa activity is linear over a wide dose range of apixaban, and precision of the Rotachrom[®] assay is well within acceptable limits for use in a clinical laboratory. The dose- and concentration-related changes observed following apixaban administration are more pronounced, and less variable, with anti-FXa activity compared with clotting tests.

In patients treated with apixaban 2.5 mg twice a day following elective knee or hip replacement surgery, predicted steady-state peak and trough anti-FXa activity are 1.3 IU/mL (5th/95th percentile 0.67-2.4 IU/mL) and 0.84 IU/mL (5th/95th percentile 0.37-1.8 IU/mL), respectively, demonstrating less than a 1.6-fold fluctuation in peak-to-trough anti-FXa activity over the dosing interval.

Although treatment with apixaban at the recommended dose does not require routine monitoring of exposure, the Rotachrom[®] anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g. overdose or emergency surgery.

Apixaban has no effect on the QTc interval in humans at doses up to 50 mg.

Mechanism of Action

Apixaban is a reversible, direct and highly selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that caused negligible prolongation of prothrombin time and bleeding time in rabbits and dogs, but more than 2-fold increases in prothrombin time and bleeding time in rats.

Pharmacokinetics

Absorption

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg. Apixaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban can be taken with or without food. Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses \geq 25 mg apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of \sim 20% CV and \sim 30% CV, respectively.

Distribution

Plasma protein binding in humans is approximately 87%. The volume of distribution (V_{ss}) is approximately 21 litres.

Metabolism and Elimination

Apixaban has multiple routes of elimination. Of the administered apixaban dose in humans, approximately 25% was recovered as metabolites, with the majority recovered in faeces. Renal excretion of apixaban accounts for approximately 27% of total clearance. Additional

contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies, respectively.

Apixaban has a total clearance of about 3.3 L/h and a half-life of approximately 12 hours.

O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolised mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major drug-related component in human plasma with no active circulating metabolites present. Apixaban is a substrate of efflux transport proteins, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Special Populations

Elderly

Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32% higher. No dose adjustment is required, except for atrial fibrillation patients with two of the following criteria; age \geq 80 years, body weight \leq 60 kg, serum creatinine \geq 133 $\mu\text{mol/L}$ (see DOSAGE AND ADMINISTRATION, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation, Use in the Elderly, Use in Renal Impairment, Body Weight).

Children and Adolescents

The efficacy and safety of ELIQUIS in children and adolescents below age 18 have not been established. No data are available.

Gender

Exposure to apixaban was approximately 18% higher in females than in males. No dose adjustment is required.

Race

The results across phase I studies showed no discernible difference in apixaban pharmacokinetics between White/Caucasian, Asian and Black/African American subjects. Findings from a population pharmacokinetic analysis in patients who received apixaban were consistent with the phase I results. No dose adjustment is required.

Body Weight

Compared with apixaban exposure in subjects with body weight of 65 to 85 kg, body weight $>$ 120 kg was associated with approximately 30% lower exposure and body weight $<$ 50 kg was associated with approximately 30% higher exposure. No dose adjustment is required; except for atrial fibrillation patients with two of the following criteria; a body weight \leq 60 kg and age \geq 80 years, serum creatinine \geq 133 $\mu\text{mol/L}$ (see DOSAGE AND ADMINISTRATION).

Renal Impairment

If there is a suspicion of renal impairment, the degree of renal impairment must be determined accurately. Caution must be exercised when renal function estimates are based on eGFR.

There was no impact of impaired renal function on peak concentration of apixaban. There was an increase in apixaban exposure correlated to decrease in renal function, as assessed via measured creatinine clearance. In individuals with mild (creatinine clearance 51 – 80 mL/min), moderate (creatinine clearance 30 – 50 mL/min) and severe (creatinine clearance 15 - 29 mL/min) renal impairment, apixaban plasma concentrations (AUC) were increased 16, 29, and 44% respectively, compared to individuals with normal creatinine clearance. Renal impairment had no evident effect on the relationship between apixaban plasma concentration and anti-FXa activity.

No dose adjustment is necessary in patients with mild or moderate renal impairment.

As there is no clinical experience in patients with renal impairment < 15 mL/min or in patients undergoing dialysis ELIQUIS is contraindicated in these patients. There is limited experience in patients with renal impairment 15 mL to < 25 mL/min with increased apixaban exposure, therefore, ELIQUIS is also contraindicated in these patients (see CONTRAINDICATIONS).

Dose adjustment is recommended for atrial fibrillation patients with two of the following criteria; serum creatinine \geq 133 μ mol/L, age \geq 80 years, body weight \leq 60 kg (see DOSAGE AND ADMINISTRATION, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation and PRECAUTIONS, Renal Impairment).

Hepatic Impairment

Apixaban has not been studied in patients with severe hepatic impairment or active hepatobiliary disease. Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS).

No dose adjustment is required in patients with mild or moderate hepatic impairment; however, given the limited number of subjects studied, caution is advised when using ELIQUIS in this population (see DOSAGE AND ADMINISTRATION, Use in Hepatic Impairment and PRECAUTIONS, Use in Hepatic Impairment).

In a study comparing subjects with mild and moderate hepatic impairment (classified as Child-Pugh A and B, respectively) to healthy control subjects, the single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in subjects with hepatic impairment. Changes in anti-FXa activity and INR were comparable between subjects with mild to moderate hepatic impairment and healthy subjects.

Pharmacokinetic/Pharmacodynamic Relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between apixaban plasma concentration and several PD endpoints (anti-FXa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0.5 - 50 mg). The relationship between apixaban plasma concentration and anti-FXa activity was best described by a linear model. The PK/PD relationship observed in patients who received apixaban in phase II or phase III clinical studies was consistent with that established in healthy subjects.

CLINICAL TRIALS

Prevention of VTE: Elective Total Hip or Total Knee Replacement Surgery

The apixaban clinical program was designed to demonstrate the efficacy and safety of apixaban for the prevention of venous thromboembolic events (VTE) in a broad range of adult patients undergoing elective hip or knee replacement. A total of 8,464 patients were randomised in two pivotal, double-blind, multi-national studies, comparing apixaban 2.5 mg given orally twice daily (4,236 patients) or enoxaparin 40 mg once daily (4,228 patients). Included in this total were 1,262 patients (618 in the apixaban group) of age 75 or older, 1,004 patients (499 in the apixaban group) with low body weight (≤ 60 kg), 1,495 patients (743 in the apixaban group) with BMI ≥ 33 kg/m² and 437 patients with severe or moderate renal impairment (217 patients in the apixaban group). The ADVANCE-3 study included 5,407 patients undergoing elective hip replacement (mean age: 61 years; 53% female), and the ADVANCE-2 study included 3,057 patients undergoing elective knee replacement (mean age: 66 years; 72% female). Apixaban was not studied in patients undergoing hip fracture surgery.

Adult patients scheduled for hip or knee replacement surgery could be enrolled provided they had no active bleeding or high risk of bleeding, no active hepatobiliary disease, their creatinine clearance was not less than 30 mL/min, their ALT or AST level was not greater than twice the upper limit of normal (ULN) and they were not on treatment with medications affecting coagulation or platelet function unless they could be withdrawn.

Subjects received either apixaban 2.5 mg given orally twice daily (po bid) or enoxaparin 40 mg administered subcutaneously once daily (sc od). The first dose of apixaban was given 12 to 24 hours post-surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Both apixaban and enoxaparin were given for 32-38 days in the ADVANCE-3 study and for 10-14 days in the ADVANCE-2 study.

Based on patient medical history in the studied population of ADVANCE-3 and ADVANCE-2 (8,464 patients), 46% had hypertension, 10% had hyperlipidemia, 9% had diabetes, and 8% had coronary artery disease.

Efficacy analyses of the pivotal studies utilised a pre-specified testing sequence that allowed testing for superiority on the primary endpoint only after non-inferiority (NI) was established. The NI margin used for the primary endpoint was 1.25, i.e. the upper bound of the 95% confidence interval (CI) for the relative risk was not to exceed 1.25. Similarly, testing for superiority on the key secondary endpoint of Major VTE was only conducted after non-inferiority on this endpoint was established.

Apixaban demonstrated a statistically superior reduction in the primary endpoint, a composite of all VTE/all cause death, and in the Major VTE endpoint, a composite of proximal deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and VTE-related death, compared to enoxaparin in both elective hip or knee replacement surgery (see Table 1).

Table 1: Efficacy results from pivotal phase III studies

| Study | ADVANCE-3 (hip) | | | ADVANCE-2 (knee) | | |
|---|------------------|--------------|---------|------------------|----------------|---------|
| | Apixaban | Enoxaparin | p-value | Apixaban | Enoxaparin | p-value |
| Study treatment | Apixaban | Enoxaparin | | Apixaban | Enoxaparin | |
| Dose | 2.5 mg po bid | 40 mg sc od | | 2.5 mg po bid | 40 mg sc od | |
| Duration of treatment | 35 ± 3 d | 35 ± 3 d | | 12 ± 2 d | 12 ± 2 d | |
| Total VTE/all-cause death | | | | | | |
| Number of events/subjects | 27/1949 | 74/1917 | <0.0001 | 147/976 | 243/997 | <0.0001 |
| Event Rate (%) | 1.39 | 3.86 | | 15.06 | 24.37 | |
| Relative Risk | 0.36 | | | 0.62 | | |
| 95% CI | (0.22, 0.54) | | | (0.51, 0.74) | | |
| Absolute Risk Difference (%) | -2.47 | | | -9.27 | | |
| 95% CI | (-3.54,- 1.50) | | | (-12.74, -5.79) | | |
| Components of primary endpoint^a | | | | | | |
| Distal or proximal DVT | | | | | | |
| Event rate (%) | 1.13 | 3.56 | | 14.62 | 24.37 | |
| 95% CI | (0.74, 1.72) | (2.81, 4.50) | | (12.54, 17.00) | (21.81, 27.14) | |
| Non-fatal PE | | | | | | |
| Event rate (%) | 0.07 | 0.19 | | 0.20 | 0.00 | |
| 95% CI | (0.00, 0.29) | (0.07, 0.45) | | (0.04, 0.61) | (0.00, 0.31) | |
| All-cause death | | | | | | |
| Event rate (%) | 0.11 | 0.04 | | 0.13 | 0.0 | |
| 95% CI | (0.02, 0.35) | (0.00, 0.24) | | (0.01, 0.52) | (0.00, 0.31) | |
| Major VTE | | | | | | |
| Number of events/subjects | 10/2199 | 25/2195 | 0.0107 | 13/1195 | 26/1199 | 0.0373 |
| Event Rate (%) | 0.45 | 1.14 | | 1.09 | 2.17 | |
| Relative Risk | 0.40 | | | 0.50 | | |
| 95% CI | (0.15, 0.80) | | | (0.26, 0.97) | | |
| Absolute Risk Difference (%) | -0.68 | | | -1.04 | | |
| 95% CI | (-1.27,- 0.17) | | | (-2.03, -0.05) | | |
| Components of Major VTE endpoint^a | | | | | | |
| Proximal DVT | | | | | | |
| Event rate (%) | 0.32(0.14, 0.68) | 0.91 | | 0.76(0.38, 1.46) | 2.17 | |
| 95% CI | | (0.59, 1.42) | | | (1.47, 3.18) | |
| Non-fatal PE | | | | | | |
| Event rate (%) | 0.07 | 0.19 | | 0.20 | 0.00 | |
| 95% CI | (0.00, 0.29) | (0.07, 0.45) | | (0.04, 0.61) | (0.00, 0.31) | |

Attachment 1: Product information for AusPAR Eliquis Apixaban Bristol-Myers Squibb Australia Pty Ltd PM-2011-03165-3-3 Date of Finalisation 21 June 2013. This Product Information was approved at the time this AusPAR was published.

| Study | ADVANCE-3 (hip) | | | ADVANCE-2 (knee) | | |
|-----------------------|-----------------|--------------|---------|------------------|--------------|---------|
| | Apixaban | Enoxaparin | p-value | Apixaban | Enoxaparin | p-value |
| Study treatment | Apixaban | Enoxaparin | | Apixaban | Enoxaparin | |
| Dose | 2.5 mg po bid | 40 mg sc od | | 2.5 mg po bid | 40 mg sc od | |
| Duration of treatment | 35 ± 3 d | 35 ± 3 d | | 12 ± 2 d | 12 ± 2 d | |
| VTE-related death | | | | | | |
| Event rate (%) | 0.04 | 0.00 | | 0.07 | 0.00 | |
| 95% CI | (0.00, 0.24) | (0.00, 0.18) | | (0.00, 0.42) | (0.00, 0.31) | |

^a Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints

The safety endpoints of major bleeding, the composite of major and clinically relevant non-major (CRNM) bleeding, and all bleeding showed similar rates for patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see Table 2). Major bleeding was defined as a decrease in haemoglobin of 20 g/L or more over a 24 hour period, transfusion of 2 or more units of packed red cells, bleeding into a critical site (e.g., intracranial haemorrhage) or fatal. CRNM bleeding was defined as significant epistaxis, gastrointestinal bleed, significant haematuria, significant haematoma, bruising or ecchymosis, or haemoptysis. All the bleeding criteria included surgical site bleeding.

In both Phase III studies, bleeding was assessed beginning with the first dose of double-blind study medication, which was either enoxaparin or injectable placebo, given 9 to 15 hours before surgery. Bleeding during the treatment period included events that occurred before the first dose of apixaban, which was given 12-24 hours after surgery. Bleeding during the post-surgery treatment period only included events occurring after the first dose of study medication after surgery. Over half the occurrences of major bleeding in the apixaban group occurred prior to the first dose of apixaban. Table 2 shows the bleeding results from the treatment period and the post-surgery treatment period.

Table 2: Bleeding results from pivotal phase III studies†

| | ADVANCE-3 | | ADVANCE-2 | |
|---|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| | Apixaban 2.5 mg po bid 35 ± 3 d | Enoxaparin 40 mg sc od 35 ± 3 d | Apixaban 2.5 mg po bid 12 ± 2 d | Enoxaparin 40 mg sc od 12 ± 2 d |
| All treated | n = 2673 | n = 2659 | n = 1501 | n = 1508 |
| | n (%) | n (%) | n (%) | n (%) |
| <i>Treatment Period</i> | | | | |
| Major | 22 (0.8) | 18 (0.7) | 9 (0.6) | 14 (0.9) |
| Fatal | 0 | 0 | 0 | 0 |
| Major + CRNM | 129 (4.8) | 134 (5.0) | 53 (3.5) | 72 (4.8) |
| All | 313 (11.7) | 334 (12.6) | 104 (6.9) | 126 (8.4) |
| <i>Post-surgery treatment period</i> | | | | |
| Major | 9 (0.3) | 11 (0.4) | 4 (0.3) | 9 (0.6) |
| Fatal | 0 | 0 | 0 | 0 |
| Major + CRNM | 96 (3.6) | 115 (4.3) | 41 (2.7) | 56 (3.7) |
| All | 261 (9.8) | 293 (11.0) | 89 (5.9) | 103 (6.8) |

† all the bleeding criteria included surgical site bleeding

Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation

The clinical program was designed to demonstrate the efficacy and safety of apixaban for the prevention of stroke and systemic embolism in patients suitable for vitamin K antagonists (VKA) (ARISTOTLE) and in patients unsuitable for VKA (AVERROES).

Both studies were active-controlled (vs. warfarin in ARISTOTLE and vs. acetylsalicylic acid (ASA) in AVERROES), randomised, double-blind, parallel-arm, multi-national studies in patients with nonvalvular, persistent, paroxysmal, or permanent atrial fibrillation (AF) or atrial flutter (AFI) and one or more of the following additional risk factors:

- prior stroke or transient ischaemic attack (TIA) (also prior systemic embolism in ARISTOTLE)
- age ≥75 years
- arterial hypertension requiring treatment
- diabetes mellitus
- heart failure ≥New York Heart Association Class 2
- decreased left ventricular ejection fraction (LVEF)
- documented peripheral arterial disease (AVERROES only).

Adult patients could be enrolled provided they had no AF due to reversible causes, clinically significant (moderate or severe) mitral stenosis, no contraindication to anticoagulation, no serious bleeding in the last 6 months or increased bleeding risk, no persistent, uncontrolled hypertension, no active infective endocarditis, no planned major surgery or planned AF or

flutter ablation surgery, no ischaemic stroke within 7 days, could comply with INR monitoring (ARISTOTLE), had no other condition requiring anticoagulation, their creatinine clearance was not less than 25 mL/min, their ALT or AST level was not greater than 2 x ULN nor total bilirubin greater than 1.5 x ULN, their platelet count was not less than $100 \times 10^9/L$, their haemoglobin level was not less than 90 g/L, they did not require treatment with aspirin > 165 mg/day (ARISTOTLE) and were either not on treatment with a thienopyridine (AVERROES) nor on treatment with both aspirin and a thienopyridine (ARISTOTLE).

Prohibited therapies while taking the study medication in ARISTOTLE were potent inhibitors of CYP3A4, glycoprotein (GP) IIb/IIIa inhibitors (e.g. abciximab, eptifibatide, tirofiban) or other antithrombotic agents (e.g., unfractionated heparin [UFH], low molecular weight heparin [LMWH], direct thrombin inhibitors, fondaparinux).

Patients with other valvular abnormalities, such as mitral regurgitation or aortic stenosis, were eligible to be enrolled.

Table 3: Patient demographic characteristics in the clinical studies

| | ARISTOTLE | AVERROES |
|-------------------------------------|----------------------|----------------------|
| Randomised Subjects | 18,201 | 5,598 |
| Mean Age | 69.1 | 69.9 |
| ≥ 65 years | 69.9% | 69.3% |
| ≥ 75 years | 31.2% | 33.8% |
| Gender | | |
| Male | 64.7% | 58.5% |
| Female | 35.3% | 41.5% |
| Race | | |
| White/Caucasian | 82.6% | 78.6% |
| Asian | 14.5% | 19.4% |
| Black/African American | 1.2% | 0.6% |
| Prior stroke or TIA | 18.6% | 13.6% |
| Hypertension | 87.4% | 86.4% |
| Diabetes | 25.0% | 19.6% |
| Heart failure | (or LVEF ≤40%) 35.4% | (or LVEF ≤35%) 33.7% |
| Mean CHADS₂ Score | 2.1 | 2.0 |
| CHADS ₂ ≤1 | 34.0% | 38.3% |
| CHADS ₂ =2 | 35.8% | 35.2% |
| CHADS ₂ ≥3 | 30.2% | 26.5% |

ARISTOTLE Study: Patients were randomised to treatment with apixaban (9,120 patients) 5 mg orally twice daily (or 2.5 mg twice daily in selected patients, 4.7%) or warfarin (9,081 patients), dosed to achieve a target international normalised ratio (INR) range 2.0-3.0, and treated for a median of 89.86 weeks for apixaban and 87.79 weeks for warfarin. The apixaban 2.5 mg twice daily dose was assigned to patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥133 μmol/L). 43% were VKA naive, defined as not previously received or have received ≤30 consecutive days

of treatment with warfarin or another VKA. Coronary artery disease was present in 33.2% of patients.

For patients randomised to warfarin, the median percentage of time in therapeutic range (INR 2-3) was 66%.

The primary objective of the study was to determine if apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients) was non-inferior to warfarin for the prevention of stroke (ischaemic, haemorrhagic, or unspecified) and systemic embolism. Assessments of superiority of apixaban versus warfarin were also prespecified for the primary endpoint, for death due to any cause and ISTH Major bleeding.

The key study outcomes were prespecified and tested in a sequential, hierarchical manner to conserve overall Type 1 error. Apixaban was tested compared to warfarin for: (1) non-inferiority on the composite endpoint of stroke and systemic embolism, (2) superiority on the composite endpoint of stroke and systemic embolism, (3) superiority on major bleeding, and (4) superiority on all-cause death.

Testing demonstrated non-inferiority of apixaban to warfarin on the composite of stroke and SE ($p < 0.0001$). As non-inferiority was met, ELIQUIS was tested for superiority on the composite of stroke and SE, with superiority over warfarin demonstrated (HR 0.79, 95% CI 0.66 to 0.95, $p = 0.0114$).

Statistically significant superiority was also achieved in all-cause death (see Table 4). Numeric reductions were observed for both cardiovascular (CV) and non-CV deaths.

Table 4: Key efficacy outcomes in patients with atrial fibrillation in the ARISTOTLE study

| | Apixaban N=9120 n (%/yr) | Warfarin N=9081 n (%/yr) | Hazard Ratio (95% CI) | P-Value |
|-------------------------------------|---|---|----------------------------------|---------------------------|
| Stroke or systemic embolism* | 212 (1.27) | 265 (1.60) | 0.79 (0.66, 0.95) | 0.0114 (< 0.0001)‡ |
| Stroke | | | | |
| Ischaemic or undetermined | 162 (0.97) | 175 (1.05) | 0.92 (0.74, 1.13) | |
| Haemorrhagic | 40 (0.24) | 78 (0.47) | 0.51 (0.35, 0.75) | |
| Systemic embolism | 15 (0.09) | 17 (0.10) | 0.87 (0.44, 1.75) | |
| All-cause death*† | 603 (3.52) | 669 (3.94) | 0.89 (0.80, 1.00) | 0.0465 |

* Assessed by sequential testing strategy for superiority designed to control the overall Type I error in the trial

† Secondary endpoint.

‡ P-Value for non-inferiority

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Centres were ranked *post hoc* by the percentage of time that warfarin-treated patients were in therapeutic range (INR 2-3). Findings for stroke/systemic embolism, major bleeds, and all cause mortality are shown for centres above and below the median level of INR control in Table 5. The benefits of apixaban relative to warfarin were consistent in patients enrolled at centres with INR control below or above the median.

Table 5: Centre INR control in the ARISTOTLE study

| | Centres with INR control below the median of 66% Hazard Ratio (95% Confidence Interval) | Centres with INR control above the median of 66% Hazard Ratio (95% Confidence Interval) |
|---------------------------------|--|--|
| Stroke/systemic embolism | 0.78 (0.62, 0.98) | 0.81 (0.61, 1.08) |
| Major bleed | 0.56 (0.45, 0.70) | 0.82 (0.68, 1.00) |
| All cause death | 0.86 (0.74, 1.00) | 0.93 (0.79, 1.10) |

AVERROES Study: Patients were randomised to treatment with apixaban 5 mg orally twice daily (or 2.5 mg twice daily in selected patients, 6.4%) or acetylsalicylic acid (ASA) 81 to 324 mg once daily. The selection of an ASA dose of 81, 162, 243, or 324 mg was at the discretion of the investigator with 90.5% of subjects receiving either an 81 mg (64.3%) or 162 mg (26.2%) dose at randomisation.

In the study, VKA therapy had been tried but discontinued in 40% of patients prior to enrollment. Common reasons for unsuitability for VKA therapy in the AVERROES study included unable/unlikely to obtain INRs at requested intervals (42.6%), patient refused treatment with VKA (37.4%), CHADS₂ score = 1 and physician did not recommend VKA (21.3%), patient could not be relied on to adhere to VKA medication instruction (15.0%), and difficulty/expected difficulty in contacting patient in case of urgent dose change (11.7%).

The primary objective of the study was to determine if apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) was superior to ASA (81-324 mg once daily) for preventing the composite outcome of stroke or systemic embolism. Assessments of superiority of apixaban versus ASA were also pre-specified for major vascular events (composite outcome of stroke, systemic embolism, myocardial infarction or vascular death) and for death due to any cause.

These key study outcomes were prespecified and tested in a sequential, hierarchical manner to conserve overall Type 1 error. Apixaban was tested compared with ASA for: (1) superiority on the composite endpoint of stroke and systemic embolism; (2) superiority on the composite endpoint of stroke of any type, systemic embolism, myocardial infarction or vascular death; and (3) superiority on all-cause death.

AVERROES was stopped early upon the recommendation of the trial's independent Data Monitoring Committee which found that a predefined interim analysis revealed clear evidence of apixaban providing a clinically important reduction in stroke and systemic embolism and acceptable safety profile.

In the study, apixaban demonstrated statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic or ischaemic) and systemic embolism (see Table 6). A clinically important reduction was observed in the key secondary composite endpoint of stroke, systemic embolism, myocardial infarction, or vascular death (see Table 6).

Table 6: Key efficacy outcomes in patients with atrial fibrillation in the AVERROES study

| | Apixaban N=2807 n (%/year) | ASA N=2791 n (%/year) | Hazard Ratio (95% CI) | P-Value |
|--|---|--------------------------------------|----------------------------------|----------------|
| Stroke or systemic embolism* | 51 (1.62) | 113 (3.63) | 0.45 (0.32, 0.62) | <0.0001 |
| Stroke | | | | |
| Ischaemic or undetermined | 43 (1.37) | 97 (3.11) | 0.44 (0.31, 0.63) | |
| Haemorrhagic | 6 (0.19) | 9 (0.28) | 0.67 (0.24, 1.88) | |
| Systemic embolism | 2 (0.06) | 13 (0.41) | 0.15 (0.03, 0.68) | |
| Stroke, systemic embolism, MI, or vascular death*† | 132 (4.21) | 197 (6.35) | 0.66 (0.53, 0.83) | 0.003^ |
| Myocardial infarction | 24 (0.76) | 28 (0.89) | 0.86 (0.50, 1.48) | |
| Vascular Death | 84 (2.65) | 96 (3.03) | 0.87 (0.65, 1.17) | |
| All-cause death*† | 111 (3.51) | 140 (4.42) | 0.79 (0.62, 1.02) | 0.068^ |

Due to early termination, the study was underpowered to evaluate all of the secondary endpoints.

* Assessed by sequential testing strategy designed to control the overall Type I error in the trial

† Secondary endpoint

^ not statistically significant

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints

Bleeding in Patients with Atrial Fibrillation

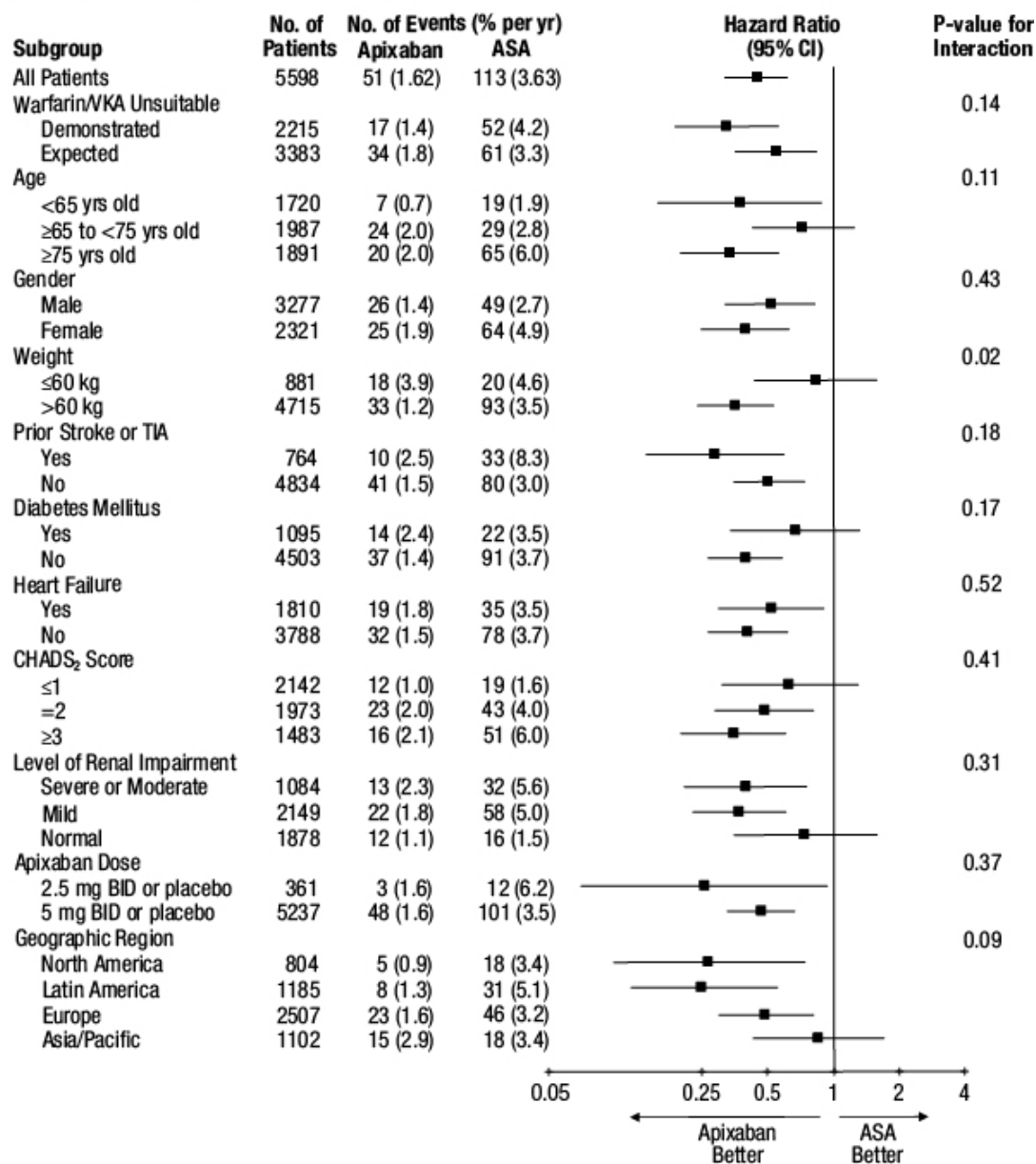
In the ARISTOTLE and AVERROES studies, the primary safety endpoint was major bleeding, which was defined as acute clinically overt bleeding that was accompanied by one or more of the following: a decrease in haemoglobin of 20 g/L or more; a transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; bleeding that is fatal. Intracranial haemorrhage included intracerebral (including haemorrhagic stroke), subarachnoid, and subdural bleeds.

Clinically relevant non-major bleeding (CRNM) was defined as acute clinically overt bleeding that does not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event and meets at least one of the following criteria: hospital admission for bleeding; physician guided medical or surgical treatment for bleeding; change in antithrombotic treatment (anticoagulant or antiplatelet) therapy.

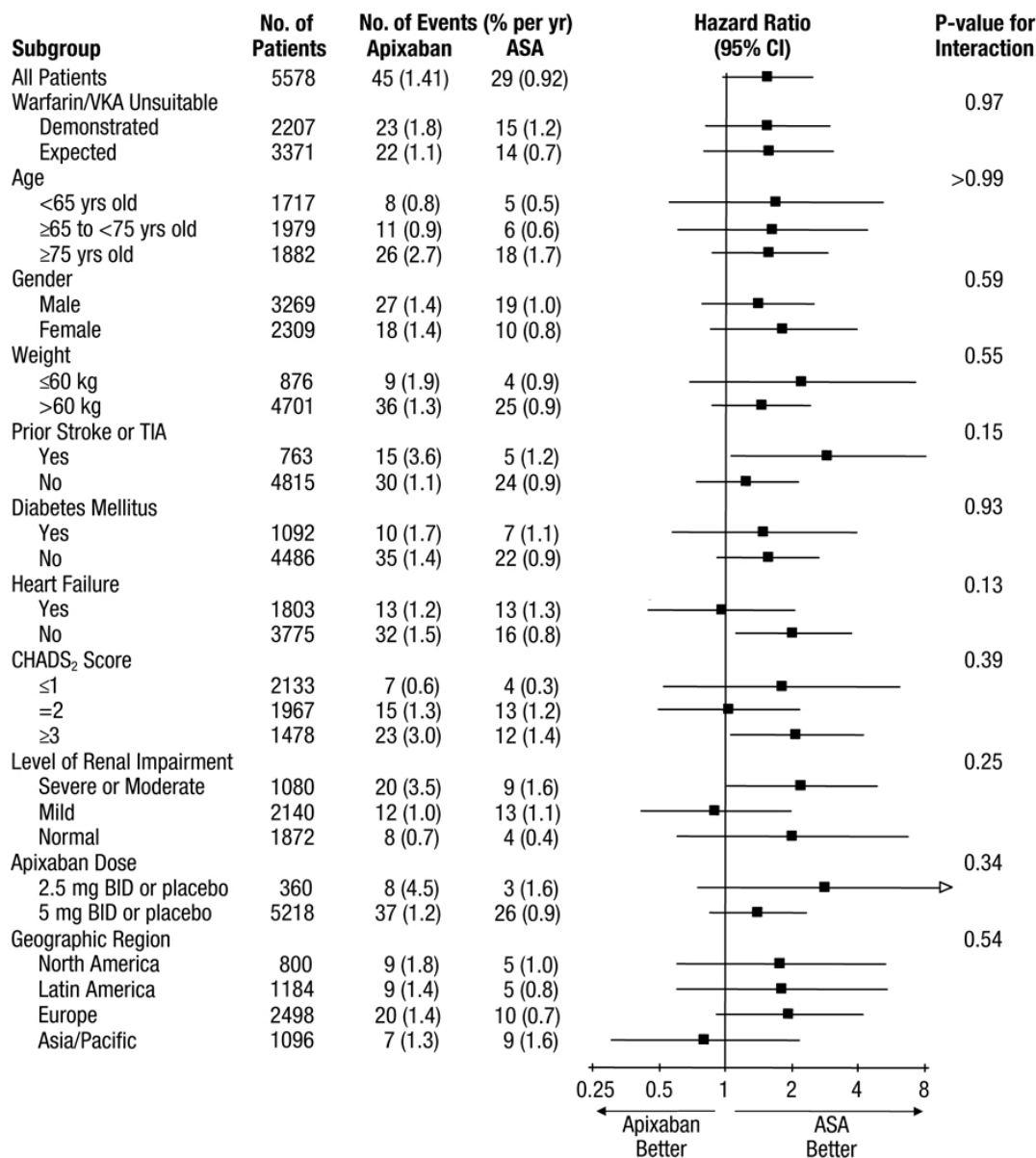
ARISTOTLE Study: There was a statistically superior reduction in the incidence of ISTH major bleeding in the apixaban treatment group compared to the warfarin treatment group (see ADVERSE EFFECTS, Table 8). There was also a significant reduction in the incidence of ISTH major+CRNM and all bleeding.

Figure 2: Stroke and systemic embolism (A), and bleeding (B) ratios by baseline characteristics - AVERROES

A. Primary Efficacy Outcome: Stroke and Systemic Embolism



B. Major Bleeding



In a clinical study in high risk acute coronary syndrome patients, as characterised by advanced age and multiple cardiac and non-cardiac co-morbidities (e.g., diabetes, heart failure), receiving apixaban 5 mg twice daily versus placebo, a significant increase in bleeding risk, including gastrointestinal and intracranial bleeding, was reported with the triple combination of apixaban, ASA and clopidogrel (see INTERACTIONS WITH OTHER MEDICINES, Effect of Other Medicines on apixaban).

INDICATIONS

ELIQUIS is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery.

ELIQUIS is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients:

- with hypersensitivity to apixaban or to any of the excipients;
- with spontaneous or pharmacological impairment of haemostasis;
- with clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding);
- with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see PHARMACOLOGY, Pharmacokinetics);
- with renal impairment creatinine clearance < 25 mL/min (see PHARMACOLOGY, Pharmacokinetics);
- receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp, such as systemic treatment with azole-antimycotics (e.g., ketoconazole) or HIV protease inhibitors (e.g., ritonavir) (see INTERACTIONS WITH OTHER MEDICINES);
- with a lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities;
- receiving concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under the circumstances of switching therapy to or from apixaban (see DOSAGE AND ADMINISTRATION) or when UHF is given at doses necessary to maintain a patent central venous or arterial catheter.

PRECAUTIONS

Haemorrhage Risk

As with all anticoagulants, ELIQUIS should be used with caution in circumstances associated with increased risk of bleeding. ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal bleeding.

Patients taking ELIQUIS are to be carefully observed for signs of bleeding complications after initiation of treatment. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

ELIQUIS administration should be discontinued if severe haemorrhage occurs (see OVERDOSAGE).

Whilst ELIQUIS is contraindicated in a number of patients (see CONTRAINDICATIONS), cautious use is recommended in patients with increased risk of haemorrhage such as:

- congenital or acquired bleeding disorders;
- bacterial endocarditis;
- thrombocytopenia;
- platelet disorders;
- history of haemorrhagic stroke;
- severe uncontrolled hypertension;
- age greater than 75 years;
- concomitant use of medications affecting haemostasis;
- bronchiectasis or history of pulmonary bleeding.

An increased risk of bleeding has been observed with increasing age (See PRECAUTIONS, Use in the Elderly) and with increased serum creatinine (see PRECAUTIONS, Renal Impairment) when apixaban was used in these patients. Patients should be made aware of signs and symptoms of blood loss and instructed to report them immediately or go to Accident and Emergency of the nearest hospital.

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist at least 24 hours after the last dose, i.e., for about two half lives. A specific antidote for ELIQUIS is not available. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration (see OVERDOSAGE). Protamine sulphate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. Because of high plasma protein binding, apixaban is not expected to be dialyzable (see PHARMACOLOGY, Pharmacokinetics).

In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate symptomatic treatments, e.g., surgical haemostasis, fluid replacement or the transfusion of fresh frozen plasma or blood products should be considered. If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant Factor VIIa may be considered. However, there is currently no experience with the use of recombinant Factor VIIa in individuals receiving apixaban. Re-dosing of recombinant Factor VIIa could be considered and titrated depending on improvement of bleeding.

There is no scientific experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no scientific rationale for reversal nor experience with systemic haemostatics (desmopressin, and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. These agents may be associated with a risk of thromboembolic complications.

Use of Thrombolytic Agents in the Treatment of Acute Ischaemic Stroke

There is very limited experience with the use of thrombolytic agents in the treatment of acute ischaemic stroke in patients administered apixaban.

Surgery and Invasive Procedures

(see DOSAGE AND ADMINISTRATION, Surgery and Invasive Procedures).

Increased Risk of Stroke with Discontinuation of ELIQUIS

An increased risk of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in patients with non-valvular atrial fibrillation. Discontinuation of apixaban prior to the onset of an effective antithrombotic effect of VKA could result in an increased risk of thrombosis. If anticoagulation with ELIQUIS must be discontinued for any reason other than pathological bleeding, consider coverage with another anticoagulant (see DOSAGE and ADMINISTRATION, Converting from or to Warfarin or Other Vitamin K Antagonists (VKA)).

Patients with Valvular Disease

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves or those with haemodynamically significant rheumatic heart disease, especially mitral stenosis. As there are no data to support that ELIQUIS provides adequate anticoagulation in patients with prosthetic heart valves, with or without atrial fibrillation, the use of ELIQUIS is not recommended in these patients.

Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment.

As there is no clinical experience in patients with renal impairment < 15 mL/min or in patients undergoing dialysis ELIQUIS is contraindicated in these patients. There is limited experience in patients with renal impairment 15 mL to < 25 mL/min with increased apixaban exposure, therefore, ELIQUIS is also contraindicated in these patients (see CONTRAINDICATIONS).

In patients with serum creatinine ≥ 133 $\mu\text{mol/L}$, the bleeding event rate of apixaban was 4.05%/years vs warfarin 5.89%/ years.

Dose adjustment is recommended in atrial fibrillation patients with two of the following criteria; serum creatinine ≥ 133 $\mu\text{mol/L}$, age ≥ 80 years, body weight ≤ 60 kg (see DOSAGE AND ADMINISTRATION, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation, Use in Renal Impairment, and PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment

ELIQUIS is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS).

ELIQUIS may be used with caution in patients with mild or moderate hepatic impairment (Child-Pugh A or B) (see DOSAGE AND ADMINISTRATION, Use in Hepatic Impairment and PHARMACOLOGY, Pharmacokinetics).

Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin ≥ 1.5 x ULN were excluded in clinical trials. Therefore ELIQUIS should be used cautiously in this population. Prior to initiating ELIQUIS, liver function testing should be performed.

Interaction with Other Medicines Affecting Haemostasis

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see CONTRAINDICATIONS).

The concomitant use of ELIQUIS with antiplatelet agents increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid (ASA), selective serotonin reuptake inhibitors, and selective noradrenaline reuptake inhibitors because these medicines may impact haemostasis. Other platelet aggregation inhibitors or other antithrombotic agents are not recommended concomitantly with ELIQUIS following surgery.

In patients with atrial fibrillation and a condition that warrants mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with ELIQUIS. In a clinical trial of patients with atrial fibrillation, concomitant use of ASA increased the major bleeding risk on apixaban from 1.8% per year to 3.4% per year and increased the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of concomitant dual antiplatelet therapy with apixaban.

An increased risk in bleeding was reported with the triple combination of apixaban, ASA and clopidogrel in a clinical study in patients with recent acute coronary syndrome (see INTERACTIONS WITH OTHER MEDICINES and CLINICAL TRIALS).

Spinal/Epidural Anaesthesia or Puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of ELIQUIS. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

There is no clinical experience with the use of apixaban with indwelling intrathecal or epidural catheters. In case of such need and based on pharmacokinetic data, a time interval of 20-30 hours (i.e., twice the half-life) between the last dose of apixaban and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal. The next dose of apixaban may be given at least 5 hours after catheter removal. Experience with neuraxial blockade is limited and extreme caution is therefore recommended when using apixaban in the presence of neuraxial blockade.

Hip Fracture Surgery

Apixaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, ELIQUIS is not recommended in these patients.

Effects on Fertility

Studies in adult rats dosed with apixaban at up to 600 mg/kg/day (up to 10 times the clinical exposure at 2.5 mg twice daily, or 3 times at 5 mg twice daily, based on free fraction AUC) showed no effect on fertility. In the offspring of rats treated with apixaban from gestation day 6 to lactation day 20, there were decreases in female mating and fertility at ≥ 200 mg/kg/day (12 times at 2.5 mg twice daily, or 4 times at 5 mg twice daily of the human exposure based on free fraction AUC). Fertility of the female offspring was unaffected at the maternal dose of 25 mg/kg/day (3 times at 2.5 mg twice daily, or 1.2 times at 5 mg twice daily of the human exposure). There were no effects on mating or fertility of male offspring at ≥ 1000 mg/kg/day (13 times at 2.5 mg twice daily, or 5 times at 5 mg twice daily of the human exposure based on free fraction AUC). Plasma apixaban concentrations in the offspring were not measured, but high apixaban concentrations (30 times the maternal plasma AUC) were detected in milk.

Use in Pregnancy

Category C

Anticoagulants and thrombolytic agents can produce placental haemorrhage and subsequent prematurity and foetal loss. There are limited data from the use of apixaban in pregnant women. Apixaban is not recommended during pregnancy.

Embryo-foetal development studies at oral doses up to 1500, 3000 and 1500 mg/kg/day in mice, rats and rabbits, respectively, and IV doses up to 5 mg/kg/day in rabbits showed no evidence of effects on embryo-foetal development in the 3 animal species tested. Maternal exposures to apixaban in the animal studies were 20 times (mouse), 4 times (rat) and 0.3 times (rabbit) the human exposure at 5 mg twice daily, based on free fraction AUC. Very low exposure to apixaban was detected in the foetus (8-11% of the maternal plasma concentration in mice, 7% in rats and <1% in rabbits).

Use in Lactation

There are no human data on the excretion of apixaban in milk. Apixaban is a substrate of BCRP, an active transporter expressed in tissues including mammary gland alveolar epithelium. Available data in animals have shown excretion of apixaban in rat milk (milk/plasma ratio: 30). Apixaban may be excreted in human milk and a risk to newborns and infants (especially their bleeding risk) cannot be excluded. This risk does not apply to many other oral anticoagulants. A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy.

In a pre/postnatal study in rats dosed from gestation day 6 to postnatal day 20, mating and fertility of female offspring were reduced (see Effects on Fertility). Otherwise, postnatal development was unaffected at maternal doses up to 1000 mg/kg/day, with exposures up to 5 times the human exposure at 5 mg twice daily based on free fraction AUC.

Paediatric Use

The pharmacokinetics, efficacy and safety of ELIQUIS in children and adolescents below age 18 have not been established, therefore the use of apixaban is not recommended in children and adolescents.

Use in the Elderly

The co-administration of ELIQUIS with acetylsalicylic acid in elderly patients should be used cautiously because of a potentially higher bleeding risk.

The event rate of stroke in patients >75 years old was greater than those < 75 years old. Increasing age, > 75 years old, is associated with a greater risk of bleeding (all, major and CRNM) including ocular and gastrointestinal bleeding. The event rate of bleeding in patients > 80 years old with apixaban 3.62%/year vs. warfarin 4.89%/year.

The benefit of apixaban in this age group was preserved for stroke, systemic embolism and risk of bleeding when compared to warfarin.

It should be taken into consideration that increasing age may be associated with declining renal function.

Prevention of VTE: Elective Total Hip or Total Knee Replacement Surgery

No dose adjustment is necessary in elderly patients. Of the total number of subjects in clinical studies of apixaban, 50% were 65 and older, while 16 % were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation

The efficacy and safety results in elderly patients (including those ≥ 75 years) in both studies were consistent with the overall population (see CLINICAL TRIALS). In subjects ≥ 75 years of age in the pivotal study (ARISTOTLE) the Hazard Ratio for the primary efficacy endpoint of stroke and systemic embolus was 0.71 (95% CI 0.53, 0.95) in favour of apixaban compared with warfarin and the Hazard Ratio for the primary safety endpoint of ISTH Major Bleeding was 0.64 (95% CI 0.52, 0.79) also in favour of apixaban. No dose adjustment is required, except for patients with two of the following criteria; age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 133 $\mu\text{mol/L}$ (see DOSAGE AND ADMINISTRATION, Use in the Elderly).

Genotoxicity

Apixaban did not induce gene mutations in bacteria (*Salmonella typhimurium*) or chromosomal damage in mammalian cells (Chinese hamster ovary cells) *in vitro* and lymphocytes in rats *in vivo*. There was no evidence of genotoxic potential in a micronucleus test in rats. The oral doses in the rat lymphocyte chromosome aberration study at up to 600 mg/kg/day for 30 days resulted in plasma apixaban concentrations 4 times the human exposure at 5 mg twice daily based on free fraction C_{max}.

Carcinogenicity

Long term studies in mice and rats at dietary doses up to 1500 and 600 mg/kg/day, respectively, did not show any evidence of carcinogenic potential. These doses resulted in plasma apixaban concentrations 42 times (mice) and 8 times (rat) human values at 2.5 mg twice daily, or 9 to 21 times (mouse) and 3 times (rat) human values at 5 mg twice daily based on free fraction AUC.

Effects on Laboratory Tests

Clotting tests (e.g. PT, INR, and aPTT) are affected as expected by the mechanism of action of apixaban (see PHARMACOLOGY, Mechanism of Action). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability (see PHARMACOLOGY, Pharmacodynamics).

Effects on Ability to Drive and Use Machines

ELIQUIS has no or negligible influence on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

Apixaban is eliminated by renal and non-renal pathways, including metabolism and biliary excretion. Metabolism occurs mainly via CYP3A4/5. Apixaban is a substrate of efflux transport proteins; P-gp and BCRP (see PHARMACOLOGY, Pharmacokinetics).

Effect of Other Medicines on Apixaban

Strong Inhibitors of CYP3A4 and P-gp

Co-administration of apixaban with ketoconazole (400 mg once a day), a strong inhibitor of both CYP3A4 and P-gp, led to a 2-fold increase in mean apixaban AUC and a 1.6-fold increase in mean apixaban C_{max}.

Two-fold increases in apixaban plasma concentrations may lead to an increased bleeding risk and, therefore, apixaban is contraindicated in patients who are receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp, such as systemic treatment with azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole or posaconazole) or HIV protease inhibitors (e.g., ritonavir) (see CONTRAINDICATIONS).

Other Inhibitors of CYP3A4 and P-gp

Active substances that are not considered strong inhibitors of both CYP3A4 and P-gp (e.g., diltiazem, naproxen, amiodarone, verapamil, clarithromycin, quinidine), are expected to increase apixaban plasma concentration to a lesser extent. Diltiazem (360 mg once a day), for instance, considered a moderate CYP3A4 and a weak P-gp inhibitor, led to a 1.4-fold increase in mean apixaban AUC and a 1.3-fold increase in C_{max}. Naproxen (500 mg, single dose) an inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and C_{max}, respectively. No dose adjustment for apixaban is required when co-administered with less potent inhibitors of CYP3A4 and/or P-gp.

Inducers of CYP3A4 and P-gp

Co-administration of apixaban with rifampin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54% and 42% decrease in mean apixaban AUC and C_{max}, respectively. The concomitant use of apixaban with other strong CYP3A4 and P-gp inducers (e.g., phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required during concomitant therapy with such agents, however strong inducers of both CYP3A4 and P-gp should be co-administered with caution.

Increased stroke rates have been noted in atrial fibrillation patients taking these medicines with either apixaban or warfarin.

Anticoagulants, Platelet Aggregation Inhibitors and NSAIDs

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see CONTRAINDICATIONS).

After combined administration of enoxaparin (40 mg single dose) with apixaban (5 mg single dose), an additive effect on anti-FXa activity was observed.

Pharmacokinetic or pharmacodynamic interactions were not evident in healthy subjects when apixaban was co-administered with ASA325 mg once a day.

Apixaban co-administered with clopidogrel (75 mg once a day) or with the combination of clopidogrel 75 mg and ASA162 mg once daily in phase 1 studies did not show a relevant increase in bleeding time or further inhibition of platelet aggregation compared to administration of the antiplatelet agents without apixaban. Increases in clotting tests (PT, INR, and aPTT) were consistent with the effects of apixaban alone.

Naproxen (500 mg), an inhibitor of P-gp, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and C_{max} in healthy subjects, respectively. Corresponding increases in clotting tests were observed for apixaban. No changes were observed in the effect of naproxen on arachidonic acid-induced platelet aggregation and no clinically relevant prolongation of bleeding time was observed after concomitant administration of apixaban and naproxen.

Despite these findings, ELIQUIS should be used with caution when co-administered with NSAIDs (including ASA) because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, acetylsalicylic acid and clopidogrel in a clinical study in patients with acute coronary syndrome. Agents associated with serious bleeding are not recommended concomitantly with ELIQUIS, such as: thrombolytic agents, GPIIb/IIIa receptor antagonists, thienopyridines (e.g., clopidogrel) in surgical patients, dipyridamole, and dextran. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter. (see PRECAUTIONS, Interaction with Other Medicines affecting Haemostasis).

In patients with atrial fibrillation and a condition that warrants mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with ELIQUIS (see PRECAUTIONS, Interaction with Other Medicines affecting Haemostasis).

Other Concomitant Therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was co-administered with atenolol or famotidine. Co-administration of apixaban 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of apixaban. Following administration of the two drugs together, mean apixaban AUC and C_{max} were 15% and 18% lower than when administered alone. The administration of apixaban 10 mg with famotidine 40 mg had no effect on apixaban AUC or C_{max}.

Concomitant Therapies Affecting Bleeding

Patients taking apixaban may be at increased risk of bleeding when taking certain concomitant medications i.e. NSAIDs, Platelet Aggregation Inhibitors, diltiazem, amiodarone, verapamil, clarithromycin and quinidine.

Paediatric Population

Interaction studies have only been performed in adults.

Effect of Apixaban on Other Medicines

In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 (IC₅₀ > 45 µM) and weak inhibitory effect on the activity of CYP2C19 (IC₅₀ > 20 µM) at concentrations that are significantly greater than peak plasma concentrations observed in patients. Apixaban did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to 20 µM. Therefore, apixaban is not expected to alter the metabolic clearance of co-administered drugs that are metabolised by these enzymes. Apixaban is not a significant inhibitor of P-gp.

In studies conducted in healthy subjects, as described below, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, or atenolol.

Digoxin

Co-administration of apixaban (20 mg once a day) and digoxin (0.25 mg once a day), a P-gp substrate, did not affect digoxin AUC or C_{max}. Therefore, apixaban does not inhibit P-gp mediated substrate transport.

Naproxen

Co-administration of single doses of apixaban (10 mg) and naproxen (500 mg), a commonly used NSAID, did not have any effect on the naproxen AUC or C_{max}.

Atenolol

Co-administration of a single dose of apixaban (10 mg) and atenolol (100 mg), a common beta-blocker, did not alter the pharmacokinetics of atenolol.

ADVERSE EFFECTS

Prevention of VTE: Elective Total Hip or Total Knee Replacement Surgery

The safety of apixaban has been evaluated in one phase II and three phase III studies including 5,924 patients exposed to apixaban 2.5 mg twice daily undergoing major orthopaedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days. Of these, 2,673 patients undergoing hip replacement were treated for a mean duration of 34 days and 3,251 patients undergoing knee replacement were treated for a mean duration of 10 and 12 days in the phase II and III studies, respectively.

In total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. Bleeding may occur during apixaban therapy in the presence of associated risk factors such as organic lesions liable to bleed. Common adverse reactions were anaemia, haemorrhage, contusion and nausea. The overall incidences of adverse reactions of bleeding, anaemia and abnormalities of transaminases (e.g., alanine aminotransferase levels) were similar between treatment groups in the phase II and phase III studies in elective hip and knee replacement surgery. The adverse reactions should be interpreted within the surgical setting.

The use of ELIQUIS may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in posthaemorrhagic anaemia. The signs, symptoms and severity will vary according to the location and degree or extent of the

Attachment 1: Product information for AusPAR Eliquis Apixaban Bristol-Myers Squibb Australia Pty Ltd PM-2011-03165-3-3 Date of Finalisation 21 June 2013. This Product Information was approved at the time this AusPAR was published.

bleeding (see PRECAUTIONS, Haemorrhage Risk and CLINICAL TRIALS). Bleeding was assessed as a safety endpoint in the clinical trials. Similar rates were seen for major bleeding, the composite of major and clinically relevant non-major bleeding, and all bleeding in patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see CLINICAL TRIALS, Table 2).

Adverse events from the pivotal phase III studies (ADVANCE-2 and ADVANCE-3) are listed in Table 7 by system organ classification (MedDRA) and by frequency.

Table 7: Common adverse events occurring in $\geq 1\%$ of patients in either group undergoing hip or knee replacement surgery, regardless of causality

| System Organ Classification / Preferred Term | Apixaban 2.5 mg po twice daily n (%) | Enoxaparin 40 mg sc once daily n (%) |
|---|--|--|
| Number treated | 4174 (100) | 4167 (100) |
| <i>Gastrointestinal disorders</i> | | |
| Nausea | 587 (14.1) | 649 (15.6) |
| Constipation | 392 (9.4) | 441 (10.6) |
| Vomiting | 288 (6.9) | 350 (8.4) |
| Diarrhoea | 96 (2.3) | 110 (2.6) |
| Dyspepsia | 48 (1.2) | 60 (1.4) |
| <i>Injury, poisoning and procedural complications</i> | | |
| Procedural pain | 431 (10.3) | 433 (10.4) |
| Anaemia postoperative | 194 (4.6) | 196 (4.7) |
| Contusion | 63 (1.5) | 86 (2.1) |
| Procedural hypotension | 62 (1.5) | 58 (1.4) |
| Wound secretion | 58 (1.4) | 54 (1.3) |
| <i>General disorders and administration site conditions</i> | | |
| Pyrexia | 307 (7.4) | 313 (7.5) |
| Oedema peripheral | 222 (5.3) | 201 (4.8) |
| Pain | 93 (2.2) | 96 (2.3) |
| Chest pain | 46 (1.1) | 40 (1.0) |
| <i>Vascular disorders</i> | | |
| Hypotension | 299 (7.2) | 296 (7.1) |
| Deep vein thrombosis | 144 (3.5) | 217 (5.2) |
| Hypertension | 70 (1.7) | 71 (1.7) |
| Thrombosis | 70 (1.7) | 71 (1.7) |
| Haematoma | 58 (1.4) | 66 (1.6) |
| <i>Investigations</i> | | |

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| System Organ Classification / Preferred Term | Apixaban 2.5 mg po twice daily n (%) | Enoxaparin 40 mg sc once daily n (%) |
|--|---|---|
| Haemoglobin decreased | 142 (3.4) | 171 (4.1) |
| Blood creatine phosphokinase increased | 102 (2.4) | 104 (2.5) |
| Body temperature increased | 85 (2.0) | 88 (2.1) |
| Aspartate aminotransferase increased | 56 (1.3) | 78 (1.9) |
| Alanine aminotransferase increased | 50 (1.2) | 77 (1.8) |
| Gamma-glutamyltransferase increased | 41 (1.0) | 72 (1.7) |
| <i>Nervous system disorders</i> | | |
| Dizziness | 207 (5.0) | 176 (4.2) |
| Headache | 87 (2.1) | 90 (2.2) |
| Somnolence | 33 (0.8) | 47 (1.1) |
| <i>Skin and subcutaneous tissue disorders</i> | | |
| Pruritus | 145 (3.5) | 137 (3.3) |
| Rash | 65 (1.6) | 67 (1.6) |
| Erythema | 49 (1.2) | 46 (1.1) |
| Blister | 44 (1.1) | 42 (1.0) |
| <i>Musculoskeletal and connective tissue disorders</i> | | |
| Arthralgia | 108 (2.6) | 87 (2.1) |
| Pain in extremity | 100 (2.4) | 79 (1.9) |
| Muscle spasms | 82 (2.0) | 85 (2.0) |
| <i>Renal and urinary disorders</i> | | |
| Urinary retention | 184 (4.4) | 169 (4.1) |
| Haematuria | 51 (1.2) | 58 (1.4) |
| <i>Psychiatric disorders</i> | | |
| Insomnia | 167 (4.0) | 163 (3.9) |
| Anxiety | 30 (0.7) | 44 (1.1) |
| <i>Infections and infestations</i> | | |
| Urinary tract infection | 80 (1.9) | 82 (2.0) |
| <i>Cardiac disorders</i> | | |
| Tachycardia | 135 (3.2) | 147 (3.5) |
| Bradycardia | 49 (1.2) | 48 (1.2) |
| <i>Respiratory, thoracic and mediastinal disorders</i> | | |
| Cough | 45 (1.1) | 41 (1.0) |

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| System Organ Classification / Preferred Term | Apixaban 2.5 mg po twice daily n (%) | Enoxaparin 40 mg sc once daily n (%) |
|--|--|--|
| Dyspnoea | 33 (0.8) | 43 (1.0) |
| <i>Blood and lymphatic system disorders</i> | | |
| Anaemia | 110 (2.6) | 131 (3.1) |
| <i>Metabolism and nutrition disorders</i> | | |
| Hypokalaemia | 50 (1.2) | 52 (1.2) |

Common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of $\geq 1\%$ to $< 10\%$ ($\geq 1/100$ to $< 1/10$):

Blood and lymphatic system disorders: anaemia (including postoperative and haemorrhagic anaemia, and respective laboratory parameters)

Vascular disorders: haemorrhage (including haematoma, and vaginal and urethral haemorrhage)

Gastrointestinal disorders: nausea

Injury, poisoning and procedural complications: contusion

Uncommon adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of $\geq 0.1\%$ to $< 1\%$ ($\geq 1/1,000$ to $< 1/100$):

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal haemorrhage (including haematemesis and melaena), haematochezia

Hepatobiliary disorders: transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal), aspartate aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: haematuria (including respective laboratory parameters)

Injury, poisoning and procedural complications: post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage

Rare or very rare adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of $< 0.1\%$ ($< 1 / 1,000$):

Gingival bleeding, haemoptysis, hypersensitivity, muscle haemorrhage, ocular haemorrhage (including conjunctival haemorrhage), rectal haemorrhage.

In the knee replacement surgery study during the intended treatment period, in the apixaban arm 4 cases of PE were diagnosed against no cases in the enoxaparin arm. No explanation can be given to this higher incidence of PE. In the hip replacement surgery study during the intended treatment period, in the apixaban arm 3 cases of PE were diagnosed against 5 cases in the enoxaparin arm (see CLINICAL TRIALS, Table 1).

Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation

The safety of apixaban has been evaluated in the ARISTOTLE and AVERROES phase III studies, including 11,284 patients exposed to apixaban 5 mg twice daily and 602 patients to 2.5 mg twice daily. The apixaban exposures were ≥ 12 months for 9,375 patients and ≥ 24 months for 3,369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89.2 weeks on apixaban and 87.5 weeks on warfarin; total patient-years for exposure was 15,534 on apixaban and 15,184 on warfarin. In AVERROES, the mean duration of exposure was approximately 59 weeks in both treatment groups; total patient-years for exposure was 3,193 on apixaban and 3,150 on ASA.

The overall discontinuation rate due to adverse reactions was 1.8% for apixaban and 2.6% for warfarin in the ARISTOTLE study, and was 1.5% for apixaban and 1.3% for ASA in the AVERROES study. The overall incidence of adverse reactions related to bleeding was numerically lower in patients on apixaban compared to warfarin in the ARISTOTLE study (24.3% vs. 31.0%) and was similar in patients on apixaban compared to ASA in the AVERROES study (9.6% vs. 8.5%).

Bleeding

Bleeding was assessed as a safety endpoint in the clinical trials. Major bleeding was defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in haemoglobin of 1.24 mmol/L or more; transfusion of 2 or more units of packed blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or bleeding that was fatal. Intracranial haemorrhage included intracerebral (haemorrhagic stroke), subarachnoid, and subdural bleeds (see CLINICAL TRIALS).

ARISTOTLE Study: There was a statistically superior reduction in the incidence of ISTH major bleeding in the apixaban treatment group compared to the warfarin treatment group. There was also a significant reduction in the incidence of ISTH major+CRNM and all bleeding.

Table 8: Bleeding events in patients with atrial fibrillation in the ARISTOTLE study

| | Apixaban N=9088 n (%/year) | Warfarin N=9052 n (%/year) | Hazard Ratio (95% CI) | P-Value |
|------------------------|---|---|----------------------------------|----------------|
| Major* | 327 (2.13) | 462 (3.09) | 0.69 (0.60, 0.80) | <0.0001 |
| Fatal# | 10 (0.06) | 37 (0.24) | 0.27 (0.13, 0.53) | - |
| Intracranial | 52 (0.33) | 125 (0.82) | 0.41 (0.30, 0.57) | - |
| Intraocular+ | 32 (0.21) | 22 (0.14) | 1.42 (0.83, 2.45) | - |
| Gastrointestinal (GI)‡ | 128 (0.83) | 141 (0.93) | 0.89 (0.70, 1.14) | - |
| Major + CRNM | 613 (4.07) | 877 (6.01) | 0.68 (0.61, 0.75) | <0.0001 |
| All | 2356 (18.1) | 3060 (25.8) | 0.71 (0.68, 0.75) | <0.0001 |

*Assessed by sequential testing strategy for superiority designed to control the overall Type I error in the trial.

Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal and extracranial bleeds and fatal haemorrhagic stroke.

+ Intraocular bleed is within the corpus of the eye (a conjunctival bleed is not an intraocular bleed).

‡ GI bleed includes upper GI, lower GI, and rectal bleeding.

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Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

Intracranial haemorrhage was reduced >50% with apixaban. GUSTO severe and TIMI major bleeding were reduced >40% with apixaban. Fatal bleeding was reduced >70% with apixaban.

Treatment discontinuation due to bleeding related adverse reactions occurred in 1.7% and 2.5% of patients treated with apixaban and warfarin, respectively.

AVERROES Study: There was an increase in the incidence of major bleeding in the apixaban treatment group compared to the ASA treatment group, which was not statistically significant. Furthermore, there was a significant increase in the Major + CRNM and all bleeding events in the subjects treated with apixaban compared with ASA. The frequency of fatal and intracranial bleeding was similar in the two treatment groups.

Table 9: Bleeding events in patients with atrial fibrillation in the AVERROES study

| | Apixaban N=2798 n (%/year) | ASA N=2780 n (%/year) | Hazard Ratio (95% CI) | p-value |
|---------------------|---|--------------------------------------|----------------------------------|----------------|
| Major | 45 (1.41) | 29 (0.92) | 1.54 (0.96, 2.45) | 0.0716 |
| Fatal | 5 (0.16) | 5 (0.16) | | |
| Intracranial | 11 (0.34) | 11 (0.35) | | |
| Major + CRNM | 140 (4.46) | 101 (3.24) | 1.38 (1.07, 1.78) | 0.0144 |
| All | 325 (10.85) | 250 (8.32) | 1.30 (1.10, 1.53) | 0.0017 |

Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.

Treatment discontinuation due to bleeding related adverse reactions occurred in 1.5% and 1.3% of patients treated with apixaban and ASA, respectively.

Adverse events from the ARISTOTLE and AVERROES studies are listed by system organ classification (MedDRA) and by frequency, in Table 10.

Table 10: Common adverse events occurring in ≥ 1% of patients in the ARISTOTLE and AVERROES studies, regardless of causality

| System Organ Classification / Preferred Term | ARISTOTLE CV185030 | | AVERROES CV185048 | |
|---|-------------------------------|---------------------------|------------------------------|----------------------|
| | Apixaban n (%) | Warfarin n (%) | Apixaban n (%) | ASA n (%) |
| Number treated | 9,088 | 9,052 | 2,798 | 2,780 |
| <i>Infections and infestations</i> | | | | |
| Nasopharyngitis | 763 (8.4) | 779 (8.6) | 89 (3.2) | 80 (2.9) |
| Urinary tract infection | 512 (5.6) | 532 (5.9) | 71 (2.5) | 57 (2.1) |
| Bronchitis | 503 (5.5) | 516 (5.7) | 80 (2.9) | 68 (2.4) |
| Upper respiratory tract infection | 436 (4.8) | 456 (5.0) | 57 (2.0) | 55 (2.0) |
| Influenza | 362 (4.0) | 333 (3.7) | 59 (2.1) | 56 (2.0) |

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| System Organ Classification / Preferred Term | ARISTOTLE CV185030 | | AVERROES CV185048 | |
|--|-----------------------|-------------------|----------------------|--------------|
| | Apixaban n (%) | Warfarin n (%) | Apixaban n (%) | ASA n (%) |
| Pneumonia | 324 (3.6) | 385 (4.3) | 61 (2.2) | 79 (2.8) |
| Sinusitis | 180 (2.0) | 161 (1.8) | - | - |
| Gastroenteritis | 145 (1.6) | 157 (1.7) | - | - |
| Cellulitis | 139 (1.5) | 179 (2.0) | 28 (1.0) | 18 (0.6) |
| Lower respiratory tract infection | 126 (1.4) | 118 (1.3) | - | - |
| Respiratory tract infection | 95 (1.0) | 101 (1.1) | - | - |
| Herpes zoster | 81 (0.9) | 91 (1.0) | - | - |
| <i>Gastrointestinal Disorders</i> | | | | |
| Diarrhoea | 585 (6.4) | 584 (6.5) | 77 (2.8) | 80 (2.9) |
| Nausea | 282 (3.1) | 286 (3.2) | 42 (1.5) | 48 (1.7) |
| Constipation | 207 (2.3) | 225 (2.5) | 35 (1.3) | 64 (2.3) |
| Vomiting | 197 (2.2) | 163 (1.8) | 21 (0.8) | 31 (1.1) |
| Abdominal pain upper | 176 (1.9) | 177 (2.0) | 50 (1.8) | 56 (2.0) |
| Abdominal pain | 172 (1.9) | 192 (2.1) | 39 (1.4) | 30 (1.1) |
| Dyspepsia | 152 (1.7) | 164 (1.8) | 26 (0.9) | 44 (1.6) |
| Gastritis | 144 (1.6) | 159 (1.8) | 46 (1.6) | 35 (1.3) |
| Toothache | 134 (1.5) | 121 (1.3) | - | - |
| Rectal haemorrhage | 125 (1.4) | 142 (1.6) | - | - |
| Gingival bleeding | 113 (1.2) | 223 (2.5) | - | - |
| <i>Respiratory, Thoracic and Mediastinal Disorders</i> | | | | |
| Dyspnoea | 605 (6.7) | 649 (7.2) | 109 (3.9) | 141 (5.1) |
| Epistaxis | 560 (6.2) | 685 (7.6) | 54 (1.9) | 52 (1.9) |
| Cough | 495 (5.4) | 505 (5.6) | 85 (3.0) | 97 (3.5) |
| Chronic obstructive pulmonary disease | 145 (1.6) | 140 (1.5) | - | - |
| Dyspnoea exertional | 104 (1.1) | 103 (1.1) | - | - |
| Haemoptysis | 85 (0.9) | 119 (1.3) | - | - |
| <i>Cardiac Disorders</i> | | | | |
| Atrial fibrillation | 496 (5.5) | 473 (5.2) | 131 (4.7) | 128 (4.6) |
| Cardiac failure | 481 (5.3) | 453 (5.0) | 89 (3.2) | 112 (4.0) |
| Cardiac failure congestive | 233 (2.6) | 245 (2.7) | 57 (2.0) | 41 (1.5) |

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| System Organ Classification / Preferred Term | ARISTOTLE CV185030 | | AVERROES CV185048 | |
|---|-----------------------|-------------------|----------------------|--------------|
| | Apixaban n (%) | Warfarin n (%) | Apixaban n (%) | ASA n (%) |
| Palpitations | 198 (2.2) | 196 (2.2) | 56 (2.0) | 60 (2.2) |
| Angina pectoris | 145 (1.6) | 133 (1.5) | 31 (1.1) | 33 (1.2) |
| Bradycardia | 132 (1.5) | 125 (1.4) | - | - |
| Angina unstable | 127 (1.4) | 98 (1.1) | - | - |
| Tachycardia | 99 (1.1) | 83 (0.9) | - | - |
| <i>Musculoskeletal and Connective Tissue Disorders</i> | | | | |
| Arthralgia | 447 (4.9) | 463 (5.1) | 69 (2.5) | 68 (2.4) |
| Back pain | 433 (4.8) | 506 (5.6) | 70 (2.5) | 64 (2.3) |
| Pain in extremity | 320 (3.5) | 325 (3.6) | 40 (1.4) | 47 (1.7) |
| Osteoarthritis | 235 (2.6) | 227 (2.5) | 35 (1.3) | 24 (0.9) |
| Muscle spasms | 171 (1.9) | 151 (1.7) | 12 (0.4) | 30 (1.1) |
| Musculoskeletal pain | 161 (1.8) | 219 (2.4) | 23 (0.8) | 28 (1.0) |
| Myalgia | 132 (1.5) | 126 (1.4) | - | - |
| Arthritis | 115 (1.3) | 116 (1.3) | - | - |
| Joint swelling | 77 (0.8) | 92 (1.0) | - | - |
| <i>Nervous System Disorders</i> | | | | |
| Dizziness | 663 (7.3) | 709 (7.8) | 109 (3.9) | 144 (5.2) |
| Headache | 482 (5.3) | 485 (5.4) | 98 (3.5) | 91 (3.3) |
| Syncope | 186 (2.0) | 150 (1.7) | 29 (1.0) | 37 (1.3) |
| Ischaemic stroke | 94 (1.0) | 81 (0.9) | 19 (0.7) | 47 (1.7) |
| Cerebrovascular accident | - | - | 17 (0.6) | 43 (1.5) |
| Transient ischaemic attack | - | - | 11 (0.4) | 36 (1.3) |
| <i>General Disorders and Administration Site Conditions</i> | | | | |
| Oedema peripheral | 611 (6.7) | 663 (7.3) | 87 (3.1) | 106 (3.8) |
| Fatigue | 392 (4.3) | 381 (4.2) | 74 (2.6) | 68 (2.4) |
| Chest pain | 347 (3.8) | 357 (3.9) | 72 (2.6) | 78 (2.8) |
| Asthenia | 217 (2.4) | 202 (2.2) | 41 (1.5) | 39 (1.4) |
| Pyrexia | 155 (1.7) | 136 (1.5) | - | - |
| Chest discomfort | 96 (1.1) | 101 (1.1) | 19 (0.7) | 29 (1.0) |
| <i>Injury, Poisoning and Procedural Complications</i> | | | | |
| Fall | 321 (3.5) | 395 (4.4) | 55 (2.0) | 62 (2.2) |

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| System Organ Classification / Preferred Term | ARISTOTLE CV185030 | | AVERROES CV185048 | |
|--|-----------------------|-------------------|----------------------|--------------|
| | Apixaban n (%) | Warfarin n (%) | Apixaban n (%) | ASA n (%) |
| Contusion | 301 (3.3) | 482 (5.3) | 35 (1.3) | 48 (1.7) |
| Laceration | 160 (1.8) | 178 (2.0) | - | - |
| <i>Investigations</i> | | | | |
| Blood glucose increased | 143 (1.6) | 123 (1.4) | - | - |
| Blood pressure increased | 134 (1.5) | 138 (1.5) | 32 (1.1) | 19 (0.7) |
| Blood creatinine increased | 132 (1.5) | 143 (1.6) | - | - |
| Blood creatine phosphokinase increased | 100 (1.1) | 123 (1.4) | 22 (0.8) | 28 (1.0) |
| Gamma-glutamyltransferase increased | 98 (1.1) | 111 (1.2) | - | - |
| <i>Vascular Disorders</i> | | | | |
| Hypertension | 386 (4.2) | 409 (4.5) | 80 (2.9) | 104 (3.7) |
| Haematoma | 224 (2.5) | 424 (4.7) | - | - |
| Hypotension | 196 (2.2) | 169 (1.9) | 32 (1.1) | 28 (1.0) |
| Haemorrhage | 106 (1.2) | 122 (1.3) | - | - |
| <i>Metabolism and Nutrition Disorders</i> | | | | |
| Gout | 210 (2.3) | 222 (2.5) | 33 (1.2) | 27 (1.0) |
| Diabetes mellitus | 179 (2.0) | 191 (2.1) | 32 (1.1) | 24 (0.9) |
| Hyperglycaemia | 119 (1.3) | 100 (1.1) | - | - |
| Decreased appetite | 106 (1.2) | 88 (1.0) | 28 (1.0) | 25 (0.9) |
| Hypokalaemia | 105 (1.2) | 106 (1.2) | - | - |
| <i>Skin and Subcutaneous Tissue Disorders</i> | | | | |
| Rash | 185 (2.0) | 194 (2.1) | 39 (1.4) | 28 (1.0) |
| Pruritis | 184 (2.0) | 139 (1.5) | 37 (1.3) | 29 (1.0) |
| Ecchymosis | 140 (1.5) | 228 (2.5) | - | - |
| <i>Renal and Urinary Disorders</i> | | | | |
| Haematuria | 338 (3.7) | 408 (4.5) | 30 (1.1) | 17 (0.6) |
| Renal failure | 107 (1.2) | 103 (1.1) | - | - |
| <i>Eye Disorders</i> | | | | |
| Cataract | 180 (2.0) | 184 (2.0) | - | - |
| Conjunctival haemorrhage | 103 (1.1) | 206 (2.3) | - | - |
| <i>Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)</i> | | | | |

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| System Organ Classification / Preferred Term | ARISTOTLE CV185030 | | AVERROES CV185048 | |
|--|-----------------------|-------------------|----------------------|--------------|
| | Apixaban n (%) | Warfarin n (%) | Apixaban n (%) | ASA n (%) |
| Basal cell carcinoma | 79 (0.9) | 95 (1.0) | - | - |
| <i>Psychiatric Disorders</i> | | | | |
| Insomnia | 160 (1.8) | 159 (1.8) | 32 (1.1) | 35 (1.3) |
| Depression | 119 (1.3) | 95 (1.0) | 23 (0.8) | 32 (1.2) |
| <i>Blood and Lymphatic System Disorders</i> | | | | |
| Anaemia | 270 (3.0) | 265 (2.9) | 41 (1.5) | 44 (1.6) |
| <i>Ear and Labyrinth Disorders</i> | | | | |
| Vertigo | 174 (1.9) | 182 (2.0) | 38 (1.4) | 35 (1.3) |
| <i>Surgical and Medical Procedures</i> | | | | |
| Tooth extraction | - | - | 29 (1.0) | 30 (1.1) |

- adverse event not reported at a frequency of $\geq 1\%$ in either treatment arm in this trial

Adverse reactions in the ARISTOTLE and AVERROES studies are listed below by system organ classification (MedDRA) and by frequency. The frequency assignments are primarily based on the frequencies observed in the ARISTOTLE study. The adverse reactions observed in the AVERROES study were consistent with those observed in the ARISTOTLE study.

Common adverse reactions in apixaban-treated patients with AF occurring at a frequency of $\geq 1\%$ to $< 10\%$ ($\geq 1/100$ to $< 1/10$):

Eye disorders: eye haemorrhage (including conjunctival haemorrhage)

Vascular disorders: other haemorrhage, haematoma

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal haemorrhage (including haematemesis and melaena), rectal haemorrhage, gingival bleeding

Renal and urinary disorders: haematuria

Injury, poisoning and procedural complications: contusion

Uncommon adverse reactions in apixaban-treated patients with AF occurring at a frequency of $\geq 0.1\%$ to $< 1\%$ ($\geq 1/1,000$ to $< 1/100$):

Immune system disorders: hypersensitivity (including drug hypersensitivity such as skin rash and anaphylactic reaction such as allergic oedema)

Nervous system disorders: brain haemorrhage, other intracranial or intraspinal haemorrhage (including subdural haematoma, subarachnoid haemorrhage, and spinal haematoma)

Vascular disorders: intra-abdominal haemorrhage

Respiratory, thoracic and mediastinal disorders: haemoptysis

Gastrointestinal disorders: haemorrhoidal haemorrhage, haematochezia, mouth haemorrhage

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Reproductive system and breast disorders: abnormal vaginal haemorrhage, urogenital haemorrhage

General disorders and administration site conditions: application site bleeding

Investigations: occult blood positive

Injury, poisoning and procedural complications: traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage

Rare adverse reactions in apixaban-treated patients with AF occurring at a frequency of $\geq 0.01\%$ to $< 0.1\%$ ($\geq 1 / 10,000$ to $< 1 / 1,000$):

Respiratory, thoracic and mediastinal disorders: respiratory tract haemorrhage (including pulmonary alveolar haemorrhage, laryngeal haemorrhage, and pharyngeal haemorrhage)

Gastrointestinal disorders: retroperitoneal haemorrhage.

DOSAGE AND ADMINISTRATION

ELIQUIS can be taken with or without food.

Missed Dose

If a dose of ELIQUIS is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and twice daily administration should be resumed. The dose should not be doubled to make up for the missed dose.

Prevention of VTE: Elective Total Hip or Total Knee Replacement Surgery

The recommended dose of ELIQUIS is 2.5 mg taken twice daily. The initial dose should be taken 12 to 24 hours after surgery.

In patients undergoing hip replacement surgery, the recommended duration of treatment is 32 to 38 days.

In patients undergoing knee replacement surgery, the recommended duration of treatment is 10 to 14 days.

The dosage of 2.5 mg taken twice daily and the duration specified for each type of surgery should not be exceeded.

Anti-platelet agents other than acetylsalicylic acid should be stopped prior to surgery and restarted after surgery as recommended in the anti-platelet product information documents. For patients on acetylsalicylic acid therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases.

Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation

The recommended dose of ELIQUIS is 5 mg taken twice daily.

The recommended dose of ELIQUIS is 2.5 mg taken twice daily in patients with at least two of the following characteristics:

- ≥ 80 years;
- body weight ≤ 60 kg;
- serum creatinine ≥ 133 $\mu\text{mol/L}$.

Use in Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment.

As there is no clinical experience in patients with renal impairment < 15 mL/min or in patients undergoing dialysis ELIQUIS is contraindicated in these patients. There is limited experience in patients with renal impairment 15 mL to < 25 mL/min with increased apixaban exposure, therefore, ELIQUIS is also contraindicated in these patients (see CONTRAINDICATIONS).

Dosage adjustment is needed in atrial fibrillation patients with two of the following criteria; serum creatinine \geq 133 μ mol/L, age \geq 80 years, body weight \leq 60 kg. see PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS, Renal Impairment).

Use in Hepatic Impairment

ELIQUIS may be used with caution in patients with mild or moderate hepatic impairment (Child-Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment (see PRECAUTIONS, Use in Hepatic Impairment and PHARMACOLOGY, Pharmacokinetics).

Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin \geq 1.5 x ULN were excluded in clinical trials. Therefore ELIQUIS should be used cautiously in this population. Prior to initiating ELIQUIS, liver function testing should be performed. (see PRECAUTIONS, Use in Hepatic Impairment).

ELIQUIS is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS).

Body Weight

No dose adjustment is required (see PHARMACOLOGY, Pharmacokinetics), except for atrial fibrillation patients with two of the following criteria; body weight \leq 60 kg, age \geq 80 years, serum creatinine \geq 133 μ mol/L (see DOSAGE and ADMINISTRATION - Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation).

Gender

No dose adjustment required (see PHARMACOLOGY, Pharmacokinetics).

Paediatric Use

The pharmacokinetics, efficacy and safety of ELIQUIS in children and adolescents below age 18 have not been established, therefore, the use of apixaban is not recommended in children and adolescents.

Use in the Elderly

Increasing age is associated with declining renal function (see CLINICAL TRIALS Figures 1 & 2).

In atrial fibrillation patients with two of the following criteria; age \geq 80 years, weight \leq 60 kg, creatinine clearance \geq 133 μ mol/L an adjustment in dose is required (see DOSAGE AND ADMINISTRATION, Prevention of Stroke and Systemic Embolism: Non-valvular Atrial Fibrillation and PRECAUTIONS, Elderly and Renal Impairment).

Converting From or To Parenteral Anticoagulants

In general, switching treatment from parenteral anticoagulants to ELIQUIS (and vice versa) can be done at the next scheduled dose.

Converting From or To Warfarin or Other Vitamin K Antagonists (VKA)

When converting patients from warfarin or other VKA therapy to ELIQUIS, discontinue warfarin or other VKA therapy and start ELIQUIS when the international normalised ratio (INR) is below 2.0.

When converting from ELIQUIS to warfarin or other VKA therapy, continue ELIQUIS for 48 hours after the first dose of warfarin or other VKA therapy. After 2 days of co-administration of ELIQUIS with VKA therapy, obtain an INR prior to the next scheduled dose of ELIQUIS. Continue co-administration of ELIQUIS and VKA therapy until the INR is ≥ 2.0 .

Surgery and Invasive Procedures

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where bleeding would be non-critical in location or easily controlled.

If surgery or invasive procedures cannot be delayed, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS may result in a higher risk of bleeding. In the event of haemorrhagic complications, the source of bleeding needs to be investigated and appropriate symptomatic treatment initiated (see PRECAUTIONS, Haemorrhage Risk).

If life-threatening bleeding cannot be controlled by the above measures, administration of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant Factor VIIa may be considered. However, these agents have not been evaluated in clinical studies. Re-dosing of prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant Factor VIIa could be considered and titrated depending on improvement of bleeding.

In controlled clinical trials, orally-administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice a day for 7 days or 50 mg once a day for 3 days) had no clinically relevant adverse effects.

A nonclinical study in dogs demonstrated that oral administration of activated charcoal up to 3 hours after apixaban administration reduced apixaban exposure; therefore, activated charcoal may be considered in the management of apixaban overdose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

ELIQUIS containing 2.5 mg apixaban for oral administration is available as yellow round, biconvex, film-coated tablets debossed with “893” on one side and “2½” on the other side in the following pack configurations:

- Cartons containing PVC/PVDC blisters of 10 film-coated tablets (1 blister of 10 film-coated tablets each), 20 film-coated tablets (2 blisters of 10 film-coated tablets each), 30 film-coated tablets (3 blisters of 10 film-coated tablets each) or 60 film-coated tablets (6 blisters of 10 film-coated tablets each).
- Cartons containing PVC/PVDC perforated unit dose blisters of 60 film-coated tablets (6 blisters of 10 film-coated tablets each) or 100 film-coated tablets (10 blisters of 10 film-coated tablets each).
- Cartons containing 1 PVC/PVDC blister of 14 film-coated tablets.

ELIQUIS containing 5 mg apixaban for oral administration is available as pink oval-shaped, biconvex, film-coated tablets debossed with “894” on one side and “5” on the other side in the following pack configurations:

- Cartons containing PVC/PVDC blisters of 20, 60 or 120 film-coated tablets in 2, 6 or 12 blisters of 10 film-coated tablets each, respectively.
- Cartons containing PVC/PVDC blisters of 14, 56, 112 or 168 film-coated tablets in 1, 4, 8 or 12 blisters of 14 film-coated tablets each, respectively.
- Cartons containing PVC/PVDC perforated unit dose blisters of 100 film-coated tablets (10 blisters of 10 film-coated tablets each).

Not all pack sizes and container types may be marketed.

Store below 30°C. This medicine does not require any special storage condition.

NAME AND ADDRESS OF THE SPONSOR

Bristol-Myers Squibb Australia Pty. Ltd.
ABN 33 004 333 322
4 Nexus Court, Mulgrave
Victoria 3170
Australia.

ALSO DISTRIBUTED BY:

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
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Australia.

Attachment 1: Product information for AusPAR Eliquis Apixaban Bristol-Myers Squibb Australia Pty Ltd PM-2011-03165-3-3 Date of Finalisation 21 June 2013. This Product Information was approved at the time this AusPAR was published.

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

21 July 2011.

DATE OF MOST RECENT AMENDMENT

29 April 2013.

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