תהיה בטוח שבחרת נכון

Eliquis® apixaban

פשוט לבחור במינון הנכון*:

SPAF

למניעת שבץ ותסחיף סיסטמי בחולים מבוגרים עם פרפור פרוזדורים (NVAF) וגורם סיכון אחד לפחות

מרבית המטופלים - 5 מ״ג פעמיים ביום

הפחתת מינון ל-2.5 מ״ג פעמיים ביום

בחולים העונים על לפחות **2** מתוך 3 הקריטריונים הבאים:

A ge≥80 years

B ody weight≤60 kg

C reatinine Level in the serum ≥1.5 mg/dl

בפינוי כלייתי בין 15 ל-29 מ״ל בדקה

לטיפול בקרישי דם בורידי הרגליים **(DVT)** ובכלי דם של הריאות **(PE)**

המינון המומלץ: 10 מ״ג פעמיים ביום ל-7 הימים הראשונים. מהיום ה-8 המינון המומלץ הוא 5 מ״ג פעמיים ביום למשך 3-6 חודשים**

למניעת הישנות קרישי דם בורידי הרגליים **(DVT)** ובכלי דם של הריאות **(PE)**

המינון המומלץ: 2.5 מ״ג פעמיים ביום בטיפול המשכי לאחר השלמת 6 חודשי טיפול באליקווים 5 מ״ג פעמיים ביום או בנוגד קרישה אחר.§

למניעת ארועים של פקקת ורידית:

- לאחר ניתוח יזום להחלפת מפרק הירך
- לאחר ניתוח יזום להחלפת מפרק הברך

המינון המומלץ: 2.5 מ״ג פעמיים ביום למשך 32-38 ימים

המינון המומלץ: 2.5 מ״ג פעמיים ביום למשך 10-14 ימים

*בהתאם למאושר ע״י משרד הבריאות הישראלי, בחולים מבוגרים (מעל גיל 18 שנים). **בחולים עם גורם סיכון חולף, משך הטיפול הינו לפחות 3 חודשים. § ההחלטה על משך הטיפול הינה אינדיבידואלית, לאחר הערכה של תועלת הטיפול לעומת הסיכון לדמם.

מטופלים	המלצות להתחלת טיפול באליקוויס בחולי NVAF[1,2]
חדש	התחלת טיפול באליקוויס פעמיים ביום[1]
החלפה מקומדין	הפסקת הטיפול בקומדין והתחלת טיפול באליקוויס כאשר INR<2[1]
החלפה מאספירין	הפסקת הטיפול באספירין, והתחלה מיידית של הטיפול באליקוויס[2]
החלפה מ-NOAC	הפסקת הטיפול בנוגד הקרישה מהסוג החדש והתחלת הטיפול באליקוויס מהנטילה הבאה[1,2]

הפסקת השימוש ב- Eliquis לפני פעולות כירורגיות אלקטיביות[1]

לפני פרוצדורות הכרוכות בסיכון נמוך לדימום, ההמלצה להפסיק את השימוש בתרופה **24 שעות לפחות** לפני הפעולה	לפני פרוצדורות הכרוכות בסיכון בינוני עד גבוה לדימום, ההמלצה להפסיק את השימוש בתרופה **48 שעות לפחות** לפני הפעולה

במקרה של ניתוח חירום, יש לנקוט באמצעי זהירות ולקחת בחשבון את הסיכון לדמם. יש לשקול את הכרחיות הניתוח לעומת הסיכון לדמם.

ללא צורך בניטור וללא מגבלות תזונה[1]

אין צורך בהתאמת מינון במטופלים עם ירידה קלה עד בינונית בתפקוד הכלייתי[1]

ניתן ליטול עם או בלי אוכל[1]

References: 1. Latest approved prescribing information. 2. Steffel J. et al, European Heart Journal (2018) 39, 1330–1393. Eliquis is supplied for oral administration in two strengths: 2.5 mg and 5 mg tablets. Indication: Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA class ≥ II). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Active clinically significant bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition if considered a significant risk factor for major bleeding. Concomitant treatment with any other anticoagulant agent except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter. Special warnings and precautions for use: It is recommended to be used with caution in conditions with increased risk of haemorrhage. Eliquis administration should be discontinued if severe haemorrhage occurs. The concomitant use of Eliquis with antiplatelet agents increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors or non-steroidal anti-inflammatory drugs, including acetylsalicylic acid. There is very limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered Eliquis. Safety and efficacy of Eliquis have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation, therefore, the use of Eliquis is not recommended in this setting. Eliquis is not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome, in particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). Eliquis should be discontinued at least 48 hours prior to elective surgery or invasive procedure with a moderate or high risk of bleeding or 24 hours prior surgery or invasive procedure with a low risk of bleeding. If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of Eliquis. Extreme caution is recommended when using Eliquis in the presence of neuraxial blockade. Eliquis is not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. Efficacy and safety of Eliquis in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in patients with active cancer have not been established. For the prevention of VTE in elective hip or knee replacement surgery (VTEp), the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), Eliquis is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 mL/minEliquis is not recommended in patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis. The use of Eliquis is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp. Eliquis should not be used for VTEt in patients receiving strong inducers of both CYP3A4 and P-gp. Common Adverse Reactions (≥ 1/100 to < 1/10): Anaemia, Thrombocytopenia, Haemorrhages, Hypotension, Nausea, gamma-glutamyltransferase increased, Alanine aminotransferase increased, Skin rash, and Contusion.

For further information, please refer to latest approved prescribing information.

PP-ELI-ISR-0534

מידת הערכת הסיכון על פי סולם CHA_2DS_2-VASc* [1,4]

CHA_2DS_2-VASc	גורם סיכון	ניקוד	
C	**אי ספיקת לב** סימנים/תסמינים לאי ספיקת לב או עדות אובייקטיבית למקטע פליטה נמוך של החדר השמאלי	1	☐
H	**יתר לחץ דם** לחץ דם במנוחה > 140/90 mmHg בשתי הזדמנויות לפחות או טיפול נגד יתר לחץ דם	1	☐
A_2	**גיל 75 או יותר**	2	☐
D	**סוכרת** גלוקוז בצום > 125 mg/dL או טיפול תרופתי בסוכרת	1	☐
S_2	**אירוע קודם** של שבץ מוחי, TIA או תסחיף סיסטמי	2	☐
V	**מחלה וסקולרית**, אירוע קודם של אוטם שריר הלב, מחלת כלי דם פריפריים או פלאק באבי העורקים	1	☐
A	**גיל 65-74 שנים**	1	☐
Sc	**קטגוריית מין (אישה)**	1	☐
	סה"כ ניקוד		☐

ניקוד בסולם CHA_2DS_2-VASc	0	1	2	3	4	5	6	7	8	9
סיכון לאירוע מוחי בתוך שנה	0.0%	1.3%	2.2%	3.2%	4.0%	6.7%	9.8%	9.6%	6.7%	15.2%

סיכום הנקודות המצטברות בטבלה זו מעיד על מידת הסיכון ללקות באירוע מוחי במהלך השנה הקרובה.[1,4]

* בחולים מבוגרים מעל גיל 18 שנים עם פרפור פרוזדורים שמקורו אינו במסתמי הלב.

הרשימות שלי: _____

_____

_____

Eliquis® apixaban

תהיה בטוח שבחרת נכון

קל ופשוט להתחיל טיפול עם אליקוויס[3]

אופן הנטילה למניעת שבץ בחולי פרפור פרוזדורים*

5 מ"ג פעמיים ביום - מרבית המטופלים

בוקר | ערב

2.5 מ"ג פעמיים ביום

הפחתת מינון נדרשת במקרים הבאים:

בחולים העונים על לפחות **2** מתוך 3 הקריטריונים הבאים:

Age ≥ 80 years
Body Weight ≤ 60 kg
Creatinie level in the serum ≥ 1.5 mg/dl

בפינוי כלייתי
בין 15 ל-29 מ"ל בדקה

* בחולים מבוגרים מעל גיל 18 שנים עם פרפור פרוזדורים שמקורו אינו במסתמי הלב.

הפסקת השימוש באליקוויס לפני פעולות כירורגיות אלקטיביות[3]

לפני פרוצדורות הכרוכות **בסיכון נמוך לדימום**, ההמלצה להפסיק את השימוש בתרופה **24 שעות לפחות** לפני הפעולה.

לפני פרוצדורות הכרוכות **בסיכון בינוני עד גבוה לדימום**, ההמלצה להפסיק את השימוש בתרופה **48 שעות לפחות** לפני הפעולה.

במקרה של ניתוח חירום, יש לנקוט באמצעי זהירות ולקחת בחשבון את הסיכון לדמם.
יש לשקול את הכרחיות הניתוח לעומת הסיכון לדמם.

References:
2016 1. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS, Eur Heart J (2016) 37 (38): 2893-2962. 2. MoH Website (health.gov.il) Recommendations for NHB 2019 Update.
3. Latest approved prescribing information. 4. 2010 ESC guidelines for the management of atrial fibrillation in collaboration with EACTS, Eur Heart J (2010) 31, 2369-2429.

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For further information, please refer to latest approved prescribing information.

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PP-ELI-ISR-0531

לעצמך,
היית בוחרת בטיפול
יעיל ובטוח?

עם אליקוויס
את בוחרת בשילוב
של יעילות ובטיחות בהשוואה לקומדין[2]

להתחיל ולהמשיך בטיפול עם אליקוויס,
לטיפול ולמניעת הישנות ב-DVT/PE*

טיפול פומי, עם התחלת פעולה
מהירה וללא צורך בזריקות
(LMWH)[2]

יעילות מתמשכת עם
פרופיל בטיחות מועדף,
בכל סוגי הדמם שנבדקו[3,4]

Eliquis® apixaban

*בחולים מבוגרים

Eliquis® apixaban

היעילות והבטיחות של ELIQUIS נשמרות גם בחיים האמיתיים

Effectiveness and Safety of Apixaban Versus Warfarin for the Treatment of VTE in US Clinical Practice[5]

Real Word Data Study based on 35,756 patient cohort.

Study Objectives

Provide real-world evidence on the comparative effectiveness and safety of apixaban versus warfarin (with PAC bridge therapy) in the treatment of patients with VTE

Study Design and Population

- Retrospective, observational analysis
- Data from 4 large, integrated private US databases: MarketScan, PharMetrics, Optum, and Humana
- **Study Period:** 1/9/2014 - 30/6/2017
- **Study Population:** 35,756 patients

Inclusion:
- Patients aged ≥ 18 years
  - Who had an ICD-9-CM/ICD-10-CM diagnosis code for lower-extremity DVT or PE
  - Received outpatient treatment with apixaban or warfarin (with PAC bridge therapy) within the 30-day period following the index encounter,*
  - Had continuous medical/drug coverage ≥ 6 months prior to the index encounter*

Exclusion*:
Apixaban and warfarin patients who had evidence of:
- AF/flutter, chemotherapy/radiation for malignancy, prior VTE, or history of major or CRNM bleeding during the 6 months preceding receipt of the index therapy †, active malignancy

Warfarin patients who had:
- Evidence of PAC therapy during ± 14 days from the first receipt of warfarin
- Evidence of PAC therapy beyond the 14-day period following warfarin initiation

*partial list

Analysis

- Patients were **propensity score matched 1:1**, without replacement, using the nearest-neighbor approach.
- Outcomes were compared using shared frailty models, which are an extension of CPH models that adjust for correlation from matching.
- Sensitivity analyses were conducted using all patients, IPTW, multivariable CPH models, and by evaluating each claims database separately.

Limitations

Patients who receive apixaban may be systematically different than those who receive warfarin with PAC bridge therapy, and to the extent that such differences are unobserved, study results may be biased. Data on inpatient drug utilization are not available in the databases, and thus, it is not possible to fully characterize the initial management of VTE requiring inpatient care. Definitions used for major bleeding, CRNM bleeding, and recurrent VTE have not been formally validated, and thus, their accuracy is unknown.

Definitions and Abbreviations

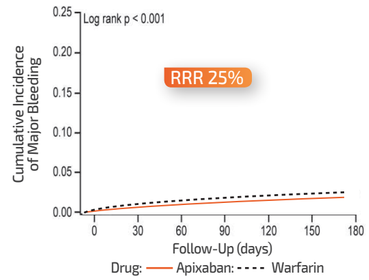
*For each patient, the earliest encounter of an ICD-9-CM/ICD-10-CM diagnosis code was designated the index encounter.
† The first treatment (eg, apixaban, warfarin) received by each patient was designated the index therapy.
Active Malignancy, Evidence of malignancy other than non-melanoma skin cancer during the 90-day period preceding receipt of the index therapy.
AF; atrial fibrillation; CPH, Cox proportional hazard; CRNM, clinically relevant nonmajor; DVT, deep vein thrombosis; GI, gastrointestinal; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICH, intracranial hemorrhage; IPTW, inverse probability of treatment weighting; PAC, parenteral anticoagulant; PE, pulmonary embolism; SD, standard deviation; US, United States; VTE, venous thromboembolism.

CRNM – clinically relevant non-major

Study Results and Conclusions:

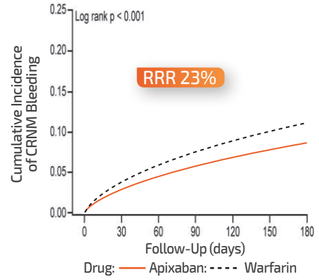
SAFETY

Main Analysis: Cumulative Incidence of **Major Bleeding** for Apixaban Versus Warfarin



Adapted from Weycker D. et al 2018[5]

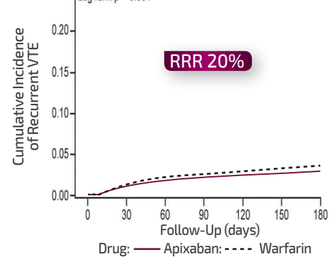
Main Analysis: Cumulative Incidence of **CRNM Bleeding** for Apixaban Versus Warfarin



Adapted from Weycker D. et al 2018[5]

EFFICACY

Main Analysis: Cumulative Incidence of **Recurrent VTE** for Apixaban Versus Warfarin



Adapted from Weycker D. et al 2018[5]

Authors' Conclusions:[5]

In this large-scale evaluation of patients who had VTE and received outpatient treatment with apixaban or warfarin in US clinical practice, risks of major bleeding, CRNM bleeding, and recurrent VTE were found to be significantly lower among patients who received apixaban compared with patient who received warfarin.

Key Patient Characteristics

A total of 17,878 apixaban patients were matched 1:1 with warfarin patients in terms of the following examples and more:

- DVT/PE
- Provoked/Unprovoked
- Setting (inpatient/ ambulatory)
- Age
- Deyo-Charlson Comorbidity Index
- Comorbidities such as:
  - Diabetes
  - Hypertension
  - Hyperlipidemia
  - Falls

Selected Patient Characteristics Comparison*

	AMPLIFY[3]	This RWD[5]
PE	34.6%	41%
Unprovoked	89.8%	77.2%
Age (mean)	57	60

* Expressed as % of total study populations

These results, which were largely comparable with and supplemental to those from the pivotal clinical trial AMPLIFY, provide the first evidence regarding the effectiveness and safety of apixaban for the treatment of VTE in real-world settings.

Reference:
1. Schulman S et al. Thrombosis and Haemostasis 2014 Apr 1;111(4):575-582. 2. Latest approved prescribing information. 3. Agnelli G et al N.Engl J Med 2013; 369:799-808. 4. European Medicines Agency Assessment Report EMA/478338/2014, 26 June 2014. 5. Weycker D. et al Thromb Heamost 2018;118:1951–1961. 6. Raskob GE et al. Thromb Haemost 2016;115:809–816. 7. Agnelli G et al.N Engl J Med. 2013;368:699-708, 8. Büller HR, et al. N Engl J Med 2012;366:1287–1297 9. Bauersachs R, et al. N Engl J Med 2010;363:2499–2510 10. Schulman S, et al. N Engl J Med 2009;361:2342–2352 11. Schulman S, et al. N Engl J Med 2013;368:709–718 12. Kearon, C et al. CHEST 2016;149 (2): 315-352. 13. Schulman S et al. Circulation 2014; 129:764-72

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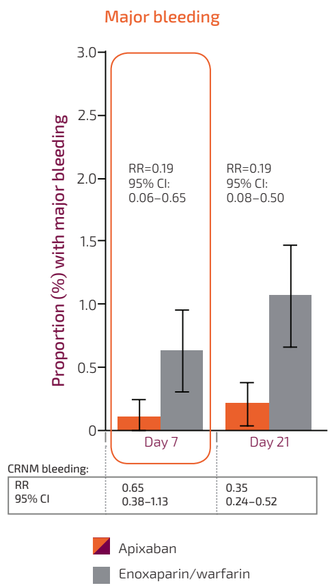
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA class ≥ II).
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults
Contraindications: Hypersensitivity to the active substance or to any of the excipients. Active clinically significant bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition if considered a significant risk factor for major bleeding. Concomitant treatment with any other anticoagulant agent except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter.
Special warnings and precautions for use: It is recommended to be used with caution in conditions with increased risk of haemorrhage. Eliquis administration should be discontinued if severe haemorrhage occurs.
The concomitant use of Eliquis with antiplatelet agents increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors or non-steroidal anti-inflammatory drugs, including acetylsalicylic acid. There is very limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered Eliquis. Safety and efficacy of Eliquis have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation, therefore, the use of Eliquis is not recommended in this setting. Eliquis is not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome, in particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). Eliquis should be discontinued at least 48 hours prior to elective surgery or invasive procedure with a moderate or high risk of bleeding or 24 hours prior surgery or invasive procedure with a low risk of bleeding. If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of Eliquis. Extreme caution is recommended when using Eliquis in the presence of neuraxial blockade. Eliquis is not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. Efficacy and safety of Eliquis in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in patients with active cancer have not been established. For the prevention of VTE in elective hip or knee replacement surgery (VTEp), the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), Eliquis is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 mL/minEliquis is not recommended in patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis. The use of Eliquis is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp. Eliquis should not be used for VTEt in patients receiving strong inducers of both CYP3A4 and P-gp.
Common Adverse Reactions (≥ 1/100 to < 1/10): Anaemia, Thrombocytopenia, Haemorrhages, Hypotension, Nausea, gamma-glutamyltransferase increased, Alanine aminotransferase increased, Skin rash, and Contusion.

For further information please refer to latest approved prescribing information.

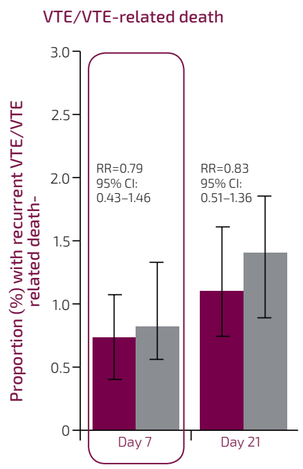
Pfizer Pharmaceuticals Israel Ltd. 9 Shenkar St., Herzeliya Pituach, Tel. 09-9700500 Fax. 09-9700501, www.pfizer.co.il

INITIAL TREATEMENT

SAFETY



EFFICACY

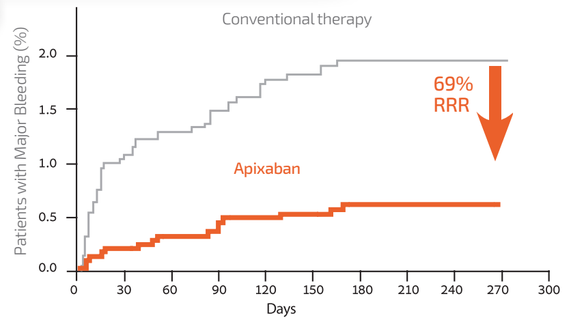


Adapted from Raskob et al. 2016[6]

Eliquis showed an early treatment effect vs LMWH/VKA in safety and efficacy primary outcomes in sub-analysis of the AMPLIFY trial.[6]

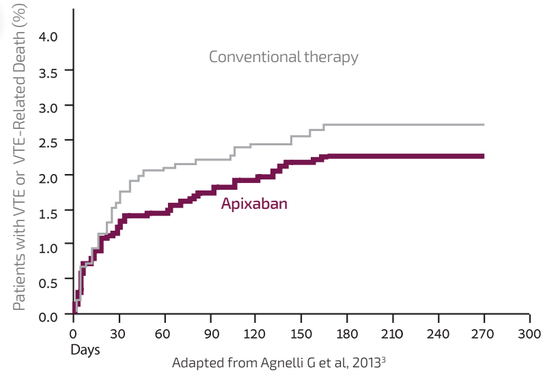
ACUTE PHASE TREATMENT

SAFETY



Eliquis patients had a 69% reduction in the risk of major bleeding vs. LMWH/VKA[3]

EFFICACY

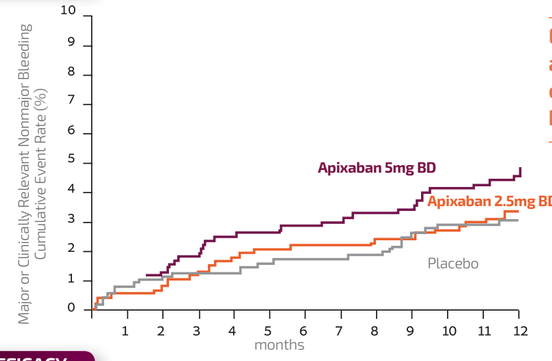


Adapted from Agnelli G et al, 2013[3]

Eliquis exhibited similar efficacy in comparison to LMWH/VKA[3]

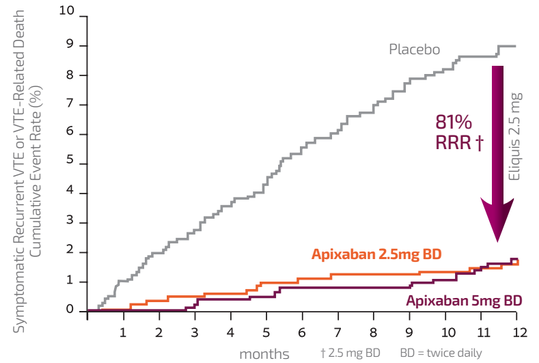
PREVENTION OF RECURRENCE

SAFETY



Eliquis demonstrated a comparable rate of Major and CRNM bleeding vs. placebo[7]

EFFICACY



Eliquis demonstrated a significant risk reduction in prevention of reccurrence of DVT/PE vs placebo [7]

Adapted from Agnelli G et al, 2013[3]

STEP 1: **START** [2] 10mg BD	STEP 2: **TREAT** [2] 5mg BD	STEP 3: **PREVENT** [2] 2.5mg BD
MORNING NIGHT	MORNING NIGHT	MORNING NIGHT
7 Days	**3-6 months**	**≥6 months**

עפ"י הקווים המנחים של ה- ACCP

Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report [12]

Based on the 2016 ACCP guidelines, in patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, **we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).**

Based on indirect comparisons: [12]

- Risk reduction of DVT/PE prevention is similar in all NOACs
- In comparison to VKA treatment, the risk of bleeding especially ICH is reduced with the NOACs
- The risk of bleeding may be lower with apixaban than with the other NOACs.

NOAC RCT Results - Acute Phase [7,8,9,10,13]

Drug	Trial	NOAC vs LMWH (%), P-value		
		Recurrent VTE + VTE death	Major Bleeding	Major + CRNM Bleeding
Eliquis (apixaban)	AMPLIFY	Non-inferiority 2.3 vs 2.7 P<0.001 (NI)	**Superiority RRR 69%** 0.6 vs 1.8 P<0.001	**Superiority RRR 56%** 4.3 vs 9.7 P<0.001
rivaroxaban	EINSTEIN-DVT	Non-inferiority 2.1 vs 3.0 P<0.001 (NI)	Not signif. 0.8 vs 1.2 P=0.21	Not signif. 8.1 vs 8.1 P=0.77
	EINSTEIN-PE	Non-inferiority 2.1 vs 1.8 P=0.003 (NI)	**Superiority RRR 51%** 1.1 vs 2.2 P=0.003	Not signif. 10.3 vs 11.4 P=0.23
dabigatran	RE-COVER**	Non-inferiority 2.4 vs 2.2 NR*	Not signif. 1.4 vs 2.0 NR*	**Superiority RRR 38%** 5.3 vs 8.5

Head-to-head studies do not exist, and direct comparisons between agents may not be made.

The duration of follow-up differed between trials therefore event rates should not be compared or interpreted as an indicator of the risk of the population. **Not significant based on 95% CI for hazard ratio. | ** Pooled analysis | NR=not reported*

NOAC RCT Results - Extended Phase [3,9,11]

Drug	Trial	NOAC vs Placebo (%), P-value		
		Recurrent VTE + VTE death	Major Bleeding	Major + CRNM Bleeding
Eliquis (apixaban 2.5mg BD)	AMPLIFY-EXT	Superiority **81% RRR** 1.7 vs 8.8 P<0.001	Not signif. 0.2 vs 0.5 NR*	Not signif. 3.2 vs 2.7 NR*
rivaroxaban	EINSTEIN-Extension	Superiority **82% RRR** 1.3 vs 7.1 P<0.001	Not signif. 0.7 vs 0 P=0.11	**Significant increase** **x5.2** 6.0 vs 1.2 P<0.001
dabigatran	RE-SONATE	Superiority **92% RRR** 0.4 vs 5.6 P<0.001	Not signif. 0.3 vs 0 P=1.0	**Significant increase** **x2.9** 5.3 vs 1.8 P=0.001

Head-to-head studies do not exist, and direct comparisons between agents may not be made.

The duration of follow-up differed between trials therefore event rates should not be compared or interpreted as an indicator of the risk of the population. **Not significant based on 95% CI for relative risk. NR=not reported.*

PP-EU-HSR-0530

Eliquis® apixaban

Oral dosing schedules across indications*:

SPAF

Prevention of stroke and systemic embolism in patients with non-valvular AF

Recommended: 5 mg BD

Dose reduction: 2.5 mg BD

In Patients who meet at least **2** of the ABC criteria:
- **A** ge≥80 years
- **B** ody weight≤60 kg
- **C** reatinine Level in the serum ≥1.5 mg/dl

Creatinine clearance 15-29 ml/min

Treatment of DVT or PE

Recommended: **10 mg BD**
for the first 7 days
Followed by: **5 mg BD** for 3-6 months **

Prevention of recurrent DVT and/or PE

Recommended: **2.5 mg BD**

Treatment should be initiated following completion of 6 months of treatment with ELIQUIS 5 mg twice daily or with another anticoagulant†.

Prevention of VTE:

–After elective hip replacement surgery
Recommended: **2.5 mg BD** for 32 to 38 days

–After elective knee replacement surgery
Recommended: **2.5 mg BD** for 10 to 14 days

*According to the ministry of health in adult patients. **As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation). †The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

BD=twice daily

Patients	Initiating and Switching recommended administration to NVAF patients[1,2]
Naive	The recommended dose of ELIQUIS is 5 mg taken orally twice daily[1]
Switching from warfarin	Discontinue warfarin therapy and start Eliquis when the international normalised ratio (INR) is < 2.0[1]
Switching from aspirin	Apixaban can be started immediately and aspirin stopped[2].
Switching from NOAC	Discontinue one being taken and begin Eliquis at the next scheduled dose[1].

Surgery and invasive procedures

Eliquis should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding.

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding.

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

Routine monitoring and food adjustments dose not required[1]

No dose adjustment necessary in patients with mild or moderate renal impairment[1]

Can be taken with or without food[1]

References: 1. Latest approved prescribing information. 2. Steffel J. et al, European Heart Journal (2018) 39, 1330–1393. Eliquis is supplied for oral administration in two strengths: 2.5 mg and 5 mg tablets. Indication: Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA class ≥ II). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Active clinically significant bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition if considered a significant risk factor for major bleeding. Concomitant treatment with any other anticoagulant agent except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter. Special warnings and precautions for use: It is recommended to be used with caution in conditions with increased risk of haemorrhage. Eliquis administration should be discontinued if severe haemorrhage occurs. The concomitant use of Eliquis with antiplatelet agents increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors or non-steroidal anti-inflammatory drugs, including acetylsalicylic acid. There is very limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered Eliquis. Safety and efficacy of Eliquis have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation, therefore, the use of Eliquis is not recommended in this setting. Eliquis is not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome, in particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). Eliquis should be discontinued at least 48 hours prior to elective surgery or invasive procedure with a moderate or high risk of bleeding or 24 hours prior surgery or invasive procedure with a low risk of bleeding. If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of Eliquis. Extreme caution is recommended when using Eliquis in the presence of neuraxial blockade. Eliquis is not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. Efficacy and safety of Eliquis in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in patients with active cancer have not been established. For the prevention of VTE in elective hip or knee replacement surgery (VTEp), the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), Eliquis is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 mL/minEliquis is not recommended in patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis. The use of Eliquis is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp. Eliquis should not be used for VTEt in patients receiving strong inducers of both CYP3A4 and P-gp. Common Adverse Reactions (≥ 1/100 to < 1/10): Anaemia, Thrombocytopenia, Haemorrhages, Hypotension, Nausea, gamma-glutamyltransferase increased, Alanine aminotransferase increased, Skin rash, and Contusion.

For further information, please refer to latest approved prescribing information.

PP-ELI-SPA-0535

كن متأكداً من صحّة اختيارك

Eliquis® apixaban

من السهل اختيار الجرعة الصحيحة[1]*:

SPAF
لمنع وتفادي النوبات والانسدادات الوريدية لدى المرضى البالغين المصابين بالرجفان الأذيني غير المرتبط بالصمامات (NVAF) وعامل خطورة واحد على الأقل

غالبية متلقي العلاج – ٥ ملغم مرتين في اليوم

لدى المرضى الذين يستوفون **2** من المعايير الـ 3 التالية على الأقل:
A ge≥80 years
B ody weight≤60 kg
C reatinine level in the serum ≥1.5 mg/dl

تخفيض الجرعة إلى 2.5 ملغم مرتين في اليوم

التصريف الكلوي بين 15 إلى 29 مل في الدقيقة

لعلاج تخثرات الدم في أوردة الرجلين **(DVT)** وفي الأوعية الدموية الرئوية **(PE)**

الجرعة الموصى بها: 10 ملغم مرتين في اليوم خلال الأيام الـ 7 الأولى. اعتبارا من اليوم الـ 8، العلاج الموصى به هو 5 ملغم مرتين في اليوم لمدة 3-6 أشهر**

لمنع وتفادي تكرار تخثرات الدم في أوردة الرجلين **(DVT)** وفي الأوعية الدموية الرئوية **(PE)**

الجرعة الموصى بها: 2.5 ملغم مرتين في اليوم خلال العلاج المتواصل بعد إتمام 6 أشهر من العلاج بواسطة إليكويس 5 ملغم مرتين في اليوم أو بأي مضاد تخثر آخر.§

لمنع وتفادي حالات الخثار الوريدي:
- بعد الجراحة المبادر إليها لاستبدال مفصل الورك
- بعد الجراحة المبادر إليها لاستبدال مفصل الركبة

الجرعة الموصى بها: 2.5 ملغم مرتين في اليوم لمدة 32-38 يوماً
الجرعة الموصى بها: 2.5 ملغم مرتين في اليوم لمدة 10-14 يوماً

* بموجب ما تمت المصادقة عليه من قبل وزارة الصحة الإسرائيلية، لدى المرضى البالغين (فوق سن 18 عاماً). ** لدى المرضى الذين لديهم عامل خطورة مؤقت، تكون مدّة العلاج 3 أشهر على الأقل. القرار بالنسبة لمدّة العلاج هو أمر فردي، بعد تقييم فوائد العلاج مقابل مخاطر حصول النزيف.

المرضى	توصيات لبدء العلاج بواسطة إليكويس لدى مرضى NVAF[1,2]
جديد	بدء العلاج بواسطة إليكويس مرتين في اليوم[1]
استبدال الكومادين	وقف العلاج بالكومادين وبدء العلاج بواسطة الإليكويس عندما يكون INR<2[1]
استبدال الأسبرين	وقف العلاج بالأسبرين، والبدء الفوري بالعلاج بواسطة إليكويس[2]
استبدال الـ NOAC	وقف العلاج بمضاد التخثر من النوع الجديد وبدء العلاج بواسطة الإليكويس اعتباراً من الجرعة التالية[1,2]

وقف استخدام Eliquis قبل الإجراءات الجراحية الاختيارية.

قبل الإجراءات الجراحية ذات مستوى الخطورة المنخفض لحصول النزيف، من الموصى به التوقف عن استخدام الدواء قبل الإجراء بـ **24 ساعة على الأقل**	قبل الإجراءات الجراحية ذات مستوى الخطورة المتوسط حتى المرتفع لحصول النزيف، من الموصى به التوقف عن استخدام الدواء قبل الإجراء بـ **48 ساعة على الأقل**
في حالات الجراحات المستعجلة (الطارئة) يجب اتخاذ إجراءات الحيطة والحذر والأخذ بعين الاعتبار مخاطر حصول النزيف.	

دون الحاجة للرقابة والقياس
ودون قيود على التغذية[1]

لا حاجة لملاءمة الجرعة لمتلقي العلاج الذين لديهم انخفاض طفيف حتى متوسط في أداء الكلى[1]

بالإمكان تناوله مع
أو بدون تناول الطعام[1]

References: 1. Latest approved prescribing information. 2. Steffel J. et al, European Heart Journal (2018) 39, 1330–1393. Eliquis is supplied for oral administration in two strengths: 2.5 mg and 5 mg tablets. Indication: Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA class ≥ II). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Active clinically significant bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition if considered a significant risk factor for major bleeding. Concomitant treatment with any other anticoagulant agent except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter. Special warnings and precautions for use: It is recommended to be used with caution in conditions with increased risk of haemorrhage. Eliquis administration should be discontinued if severe haemorrhage occurs. The concomitant use of Eliquis with antiplatelet agents increases the risk of bleeding. Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors or non-steroidal anti-inflammatory drugs, including acetylsalicylic acid. There is very limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered Eliquis. Safety and efficacy of Eliquis have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation, therefore, the use of Eliquis is not recommended in this setting. Eliquis is not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome, in particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). Eliquis should be discontinued at least 48 hours prior to elective surgery or invasive procedure with a moderate or high risk of bleeding or 24 hours prior surgery or invasive procedure with a low risk of bleeding. If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of Eliquis. Extreme caution is recommended when using Eliquis in the presence of neuraxial blockade. Eliquis is not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. Efficacy and safety of Eliquis in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in patients with active cancer have not been established. For the prevention of VTE in elective hip or knee replacement surgery (VTEp), the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), Eliquis is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 mL/min)Eliquis is not recommended in patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis. The use of Eliquis is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp. Eliquis should not be used for VTEt in patients receiving strong inducers of both CYP3A4 and P-gp. Common Adverse Reactions (≥ 1/100 to < 1/10): Anaemia, Thrombocytopenia, Haemorrhages, Hypotension, Nausea, gamma-glutamyltransferase increased, Alanine aminotransferase increased, Skin rash, and Contusion.

For further information, please refer to latest approved prescribing information.

PP-ELI-SR-0533

SUMMARY OF PRODUCT CHARACTERISTICS

Patient Card
Please provide patient safety information card (patient card) to each patient who is prescribed with Eliquis 2.5 or 5 mg. Explain to the patient the implications of anticoagulant treatment including the need for compliance. Please also explain the signs of bleeding and when to seek medical attention. The patient card will inform physicians and dentists about the patient‘s anticoagulation treatment and will contain emergency contact information. The patient should be instructed to carry the patient alert card at all times and present it to every health care provider.

1. NAME OF THE MEDICINAL PRODUCT

ELIQUIS 2.5, mg film-coated tablets
ELIQUIS 5 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg or 5mg apixaban.

Excipients with known effect:

Each 2.5 mg film-coated tablet contains 51.43 mg lactose.
Each 5 mg film-coated tablet contains 102.86 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

ELIQUIS 2.5 mg - yellow, round tablets debossed with 893 on one side and 2½ on the other side.

ELIQUIS 5 mg - pink, oval tablets debossed with 894 on one side and 5 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ELIQUIS 2.5 mg film-coated tablets
Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).

ELIQUIS 5 mg film-coated tablets

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (see section 4.4 for haemodynamically unstable PE patients).

4.2 Posology and method of administration

Posology

Prevention of VTE (VTEp): elective hip or knee replacement surgery

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

Physicians may consider the potential benefits of earlier anticoagulation for VTE prophylaxis as well as the risks of post-surgical bleeding in deciding on the time of administration within this time window.

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.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)

The recommended dose of apixaban is 5 mg taken orally twice daily.

Dose reduction

The recommended dose of apixaban is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).

Therapy should be continued long term.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)

The recommended dose of apixaban for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation).

The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant, as indicated in Table 1 below (see also section 5.1).

Table 1:

	Dosing schedule	Maximum daily dose
Treatment of DVT or PE	10 mg twice daily for the first 7 days	20 mg
	followed by 5 mg twice daily	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE	2.5 mg twice daily	5 mg

The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

Missed dose
If a dose is missed, the patient should take ELIQUIS immediately and then continue with twice daily intake as before.

Switching
Switching treatment from parenteral anticoagulants to ELIQUIS (and vice versa) can be done at the next scheduled dose (see section 4.5). These agents should not be administered simultaneously.

Switching from vitamin K antagonist (VKA) therapy to Eliquis
When converting patients from vitamin K antagonist (VKA) therapy to Eliquis, discontinue warfarin or other VKA therapy and start Eliquis when the international normalised ratio (INR) is < 2.0.

Switching from Eliquis to VKA therapy
When converting patients from Eliquis to VKA therapy, continue administration of Eliquis for at least 2 days after beginning VKA therapy. After 2 days of coadministration of Eliquis with VKA therapy, obtain an INR prior to the next scheduled dose of Eliquis. Continue coadministration of Eliquis and VKA therapy until the INR is ≥ 2.0.

Switching between Eliquis and anticoagulants other than warfarin: Discontinue one being taken and begin the other at the next scheduled dose.

Renal impairment

In patients with mild or moderate renal impairment, the following recommendations apply:

- for the prevention of VTE in elective hip or knee replacement surgery (VTEp), for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), no dose adjustment is necessary (see section 5.2).

- for the prevention of stroke and systemic embolism in patients with NVAF and serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg, a dose reduction is necessary and described above. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary (see section 5.2).

In patients with severe renal impairment (creatinine clearance 15-29 mL/min) the following recommendations apply (see sections 4.4 and 5.2):

- for the prevention of VTE in elective hip or knee replacement surgery (VTEp).
-for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) apixaban is to be used with caution;

-for the prevention of stroke and systemic embolism in patients with NVAF, patients should receive the lower dose of apixaban 2.5 mg twice daily.

In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended (see sections 4.4 and 5.2).

Hepatic impairment
ELIQUIS is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

It is not recommended in patients with severe hepatic impairment (see sections 4.4. and 5.2).

It should 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 sections 4.4 and 5.2).

Patients with elevated liver enzymes alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) >2 x ULN or total bilirubin ≥1.5 x ULN were excluded in clinical trials. Therefore ELIQUIS should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating ELIQUIS, liver function testing should be performed.

Body weight
VTEp and VTEt - No dose adjustment required (see sections 4.4 and 5.2).
NVAF - No dose adjustment required, unless criteria for dose reduction are met (see *Dose reduction* at the beginning of section 4.2).

Gender
No dose adjustment required (see section 5.2).

Elderly
VTEp and VTEt – No dose adjustment required (see sections 4.4 and 5.2).
NVAF – No dose adjustment required, unless criteria for dose reduction are met (see *Dose reduction* at the beginning of section 4.2).

Cardioversion (NVAF)
Patients can stay on apixaban while being cardioverted.

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

Method of administration
Oral use.
ELIQUIS should be swallowed with water, with or without food.

For patients who are unable to swallow whole tablets, Eliquis tablets may be crushed and suspended in water, or 5% dextrose in water (D5W), or apple juice or mixed with apple puree and immediately administered orally (see section 5.2). Alternatively, Eliquis tablets may be crushed and suspended in 60 mL of water or D5W and immediately delivered through a nasogastric tube (see section 5.2). Crushed Eliquis tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 5.2).
- Lesion or condition if considered a significant risk factor for major bleeding. This may include 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.
- 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 specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

4.4 Special warnings and precautions for use

Haemorrhage risk
As with other anticoagulants, patients taking ELIQUIS are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. ELIQUIS administration should be discontinued if severe haemorrhage occurs (see sections 4.8 and 4.9). Although treatment with apixaban does not require routine monitoring of exposure, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery (see section 5.1).

Interaction with other medicinal products affecting haemostasis
Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

The concomitant use of ELIQUIS with antiplatelet agents increases the risk of bleeding (see section 4.5).
Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) or non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid.

Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with ELIQUIS (see section 4.5).

In patients with atrial fibrillation and conditions that warrant 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 (2.1%) use of concomitant dual antiplatelet therapy.

In a clinical trial of high-risk post acute coronary syndrome patients, characterized by multiple cardiac and non-cardiac comorbidities, who received ASA or the combination of ASA and clopidogrel, a significant increase in risk of ISTH (International Society on Thrombosis and Haemostasis) major bleeding was reported for apixaban (5.13% per year) compared to placebo (2.04% per year) .

Use of Thrombolytic agents for the treatment of acute ischemic stroke
There is very limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered apixaban.

Patients with prosthetic heart valves
Safety and efficacy of Eliquis have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of Eliquis is not recommended in this setting.

Patients with antiphospholipid syndrome
Direct acting Oral Anticoagulants (DOACs) including apixaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

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 bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable.

Eliquis should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled.

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

Eliquis should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (for cardioversion see section 4.2).

Temporary discontinuation
Discontinuing anticoagulants, including ELIQUIS, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided and if anticoagulation with ELIQUIS must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

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 there is such need and based on the general PK characteristics of apixaban, a time interval of 20-30 hours (i.e., 2 x 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. As with all new anticoagulant drugs, experience with neuraxial blockade is limited and extreme caution is therefore recommended when using apixaban in the presence of neuraxial blockade.

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy
Eliquis is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of apixaban have not been established in these clinical situations.

Patients with active cancer
Efficacy and safety of apixaban in the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in patients with active cancer have not been established.

Patients with renal impairment
Limited clinical data indicate that apixaban plasma concentrations are increased in patients with severe renal impairment (creatinine clearance 15-29 mL/min) which may lead to an increased bleeding risk. For the prevention of VTE in elective hip or knee replacement surgery (VTEp), the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), apixaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 mL/min) (see sections 4.2 and 5.2).

For the prevention of stroke and systemic embolism in patients with NVAF, patients with severe renal impairment (creatinine clearance 15-29 mL/min), and patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily (see section 4.2);

In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended (see sections 4.2 and 5.2).

Elderly patients
Increasing age may increase haemorrhagic risk (see section 5.2).
Also, the co-administration of ELIQUIS with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

Body weight
Low body weight (< 60 kg) may increase haemorrhagic risk (see section 5.2).

Patients with hepatic impairment
ELIQUIS is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).
It is not recommended in patients with severe hepatic impairment (see section 5.2).
It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) (see sections 4.2 and 5.2).
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 (see section 5.2). Prior to initiating ELIQUIS, liver function testing should be performed.

Interaction with inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)
The use of ELIQUIS is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir). These medicinal products may increase apixaban exposure by 2-fold (see section 4.5), or greater in the presence of additional factors that increase apixaban exposure (e.g., severe renal impairment).

Interaction with inducers of both CYP3A4 and P-gp
The concomitant use of ELIQUIS with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in apixaban exposure. In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with coadministration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone.

In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply (see section 4.5):

- for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE, apixaban should be used with caution;

- for the treatment of DVT and treatment of PE, apixaban should not be used since efficacy may be compromised.

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, it is not recommended in these patients.

Laboratory parameters
Clotting tests (e.g., prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT)) are affected as expected by the mechanism of action of apixaban. Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability (see section 5.1).

Information about excipients
ELIQUIS contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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}.

The use of ELIQUIS is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir) (see section 4.4).

Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (eg. amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine, verapamil) are expected to increase apixaban plasma concentration to a lesser extent. No dose adjustment for apixaban is required when coadministered with agents that are not strong inhibitors of both CYP3A4 and P-gp. For example, diltiazem (360 mg once a day), , 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. Clarithromycin (500 mg, twice a day), an inhibitor of P-gp and a strong inhibitor of CYP3A4, led to a 1.6-fold and 1.3-fold increase in mean apixaban AUC and C_{max} respectively.

Inducers of CYP3A4 and P-gp
Co-administration of apixaban with rifampicin, 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 in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp apixaban should be used with caution for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE.

Apixaban is not recommended for the treatment of DVT and PE in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp since efficacy may be compromised (see section 4.4).

Anticoagulants,platelet aggregation inhibitors, SSRIs/SNRIs and NSAIDs
Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated (see section 4.3).

After combined administration of enoxaparin (40 mg single dose) with apixaban (5 mg single dose), an additive effect on anti-Factor Xa activity was observed.
Pharmacokinetic or pharmacodynamic interactions were not evident when apixaban was co-administered with ASA 325 mg once a day.

Apixaban co-administered with clopidogrel (75 mg once a day) or with the combination of clopidogrel 75 mg and ASA 162 mg once daily , or with prasugrel (60 mg followed by 10 mg once daily) in Phase 1 studies did not show a relevant increase in template 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}, 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, there may be individuals with a more pronounced pharmacodynamic response when antiplatelet agents are co-administered with apixaban. ELIQUIS should be used with caution when co-administered with SSRIs/SNRIs or NSAIDs (including acetylsalicylic acid) because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, ASA and clopidogrel in a clinical study in patients with acute coronary syndrome (see section 4.4).
Medicinal products associated with serious bleeding are not recommended concomitantly with ELIQUIS, such as: thrombolytic agents, GPIIb/IIIa receptor antagonists, thienopyridines (e.g., clopidogrel), dipyridamole, dextran and sulfinpyrazone.

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 medicinal products 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}.

Effect of apixaban on other medicinal products
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 coadministered 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.

Activated charcoal:
Administration of activated charcoal reduces apixaban exposure (see section 4.9).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of apixaban in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Apixaban is not recommended during pregnancy.

Breast-feeding
It is unknown whether apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of apixaban in milk. In rat milk, a high milk to maternal plasma ratio (C_{max} about 8, AUC about 30) was found, possibly due to active transport into the milk. A risk to newborns and infants cannot be excluded.

A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy.

Fertility
Studies in animals dosed with apixaban have shown no effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The safety of apixaban has been investigated in 7 Phase III clinical studies including more than 21,000 patients: more than 5,000 patients in VTEp studies, more than 11,000 patients in NVAF studies and more than 4,000 patients in the VTE treatment (VTEt) studies, for an average total exposure of 20 days, 1.7 years and 221 days respectively (see section 5.1).

Common adverse reactions were haemorrhage, contusion, epistaxis, and haematoma (see Table 2 for adverse event profile and frequencies by indication).

In the VTEp studies, in total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. The overall incidence of adverse reactions related to bleeding with apixaban was 10% in the apixaban vs enoxaparin studies.

In the NVAF studies, the overall incidence of adverse reactions related to bleeding with apixaban was 24.3% in the apixaban vs warfarin study and 9.6% in the apixaban vs acetylsalicylic acid study. In the apixaban vs warfarin study the incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) with apixaban was 0.76%/year. The incidence of ISTH major intraocular bleeding with apixaban was 0.18%/year.

In the VTEt studies, the overall incidence of adverse reactions related to bleeding with apixaban was 15.6% in the apixaban vs enoxaparin/warfarin study and 13.3% in the apixaban vs placebo study (see section 5.1).

Tabulated list of adverse reactions
Table 2 shows the adverse reactions ranked under headings of System Organ Class and frequency using the following convention: very common (≥1/10); common (≥1/100 to < 1/10); uncommon

(≥1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data) for VTEp, NVAF, and VTEt respectively.

Table 2

System Organ Class	**Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)**	**Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)**	**Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)**
Blood and lymphatic system disorders			
Anaemia	Common	Common	Common
Thrombocytopenia	Uncommon	Uncommon	Common
Immune system disorders			
Hypersensitivity, allergic oedema and Anaphylaxis	Rare	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon*
Nervous system disorders			
Brain haemorrhage†	Not known	Uncommon	Rare
Eye disorders			
Eye haemorrhage (including conjunctival haemorrhage)	Rare	Common	Uncommon
Vascular disorders			
Haemorrhage, haematoma	Common	Common	Common
Hypotension (including procedural hypotension)	Uncommon	Common	Uncommon
Intra-abdominal haemorrhage	Not known	Uncommon	Not known
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Uncommon	Common	Common
Haemoptysis	Rare	Uncommon	Uncommon
Respiratory tract haemorrhage	Not known	Rare	Rare
Gastrointestinal disorders			
Nausea	Common	Common	Common
Gastrointestinal haemorrhage	Uncommon	Common	Common
Haemorrhoidal haemorrhage,	Not known	Uncommon	Uncommon
mouth haemorrhage	Not known	Uncommon	Common
Haematochezia	Uncommon	Uncommon	Uncommon
Rectal haemorrhage, gingival bleeding	Rare	Common	Common
Retroperitoneal haemorrhage	Not known	Rare	Not known
Hepatobiliary disorders			
Liver function test abnormal , aspartate aminotransferase increased, , , blood alkaline phosphatase increased, blood	Uncommon	Uncommon	Uncommon

System Organ Class	Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)	Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)
bilirubin increased			
gamma-glutamyltransferase increased	Uncommon	Common	Common
Alanine aminotransferase incresed	Uncommon	Uncommon	Common
Skin and subcutaneous tissue disorders			
Skin rash	Not known	Uncommon	Common
Alopecia	Rare	Uncommon	Uncommon
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage	Rare	Rare	Uncommon
Renal and urinary disorders			
Haematuria	Uncommon	Common	Common
Reproductive system and breast disorders			
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon	Uncommon	Common
General disorders and administration site conditions			
Application site bleeding	Not known	Uncommon	Uncommon
Investigations			
Occult blood positive	Not known	Uncommon	Uncommon
Injury, poisoning and procedural complications			
Contusion	Common	Common	Common
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	Uncommon	Uncommon	Uncommon
Traumatic haemorrhage,	Not known	Uncommon	Uncommon

* There were no occurrences of generalized pruritus in CV185057 (long term prevention of VTE)

† The term "Brain haemorrhage" encompasses all intracranial or intraspinal haemorrhages (ie., haemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural haemorrhages).

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 bleeding (see sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

There is no antidote to ELIQUIS. Overdose of apixaban may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g., surgical haemostasis or the transfusion of fresh frozen plasma should be considered.

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 daily (bid) for 7 days or 50 mg once daily (od) for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively, and had no impact on C_{max}. Mean half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

If life-threatening bleeding cannot be controlled by the above measures, administration of prothrombin complex concentrates (PCCs) or recombinant factor VIIa may be considered. Reversal of Eliquis pharmacodynamic effects, as demonstrated by changes in the thrombin generation assay, was evident at the end of infusion and reached baseline values within 4 hours after the start of a 4-factor PCC 30 minute infusion in healthy subjects. However, there is no clinical experience with the use of 4-factor PCC products to reverse bleeding in individuals who have received Eliquis. Currently there is 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.

Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleedings.

Haemodialysis decreased apixaban AUC by 14% in subjects with end-stage renal disease (ESRD), when a single dose of apixaban 5 mg was administered orally. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents direct factor Xa inhibitors, ATC code: B01AF02

Mechanism of action

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, 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 preserved haemostasis.

Pharmacodynamic effects

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. In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

Apixaban also demonstrates anti-FXa activity as evident by reduction in Factor Xa enzyme activity in multiple commercial anti-FXa kits, however results differ across kits. Data from clinical trials are only available for 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 approximately linear over a wide dose range of apixaban.

Table 3 below shows the predicted steady state exposure and anti-Factor Xa activity for each indication. In patients taking apixaban for the prevention of VTE following hip or knee replacement surgery, the results demonstrate a less than 1.6-fold fluctuation in peak-to-trough levels. In nonvalvular atrial fibrillation patients taking apixaban for the prevention of stroke and systemic embolism, the results demonstrate a less than 1.7-fold fluctuation in peak-to-trough levels. In patients taking apixaban for the treatment of DVT and PE or prevention of recurrent DVT and PE, the results demonstrate a less than 2.2-fold fluctuation in peak-to-trough levels.

Table 3: Predicted Apixaban Steady-state Exposure and Anti-Xa Activity

	Apix. Cmax (ng/mL)	**Apix. Cmin (ng/mL)**	**Apix. Anti-Xa Activity Max (IU/mL)**	**Apix. Anti-Xa Activity Min (IU/mL)**
	Median [5th, 95th Percentile]			
Prevention of VTE: elective hip or knee replacement surgery				
2.5 mg twice daily	77 [41, 146]	51 [23, 109]	1.3 [0.67, 2.4]	0.84 [0.37, 1.8]
Prevention of stroke and systemic embolism: NVAF				
2.5 mg twice daily*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg twice daily	171 [91, 321]	103 [41, 230]	2.6 [1.4, 4.8]	1.5 [0.61, 3.4]
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)				
2.5 mg twice daily	67 [30, 153]	32 [11, 90]	1.0 [0.46, 2.5]	0.49 [0.17, 1.4]
5 mg twice daily	132 [59, 302]	63 [22, 177]	2.1 [0.91, 5.2]	1.0 [0.33, 2.9]
10 mg twice daily	251 [111, 572]	120 [41, 335]	4.2 [1.8, 10.8]	1.9 [0.64, 5.8]

* Dose adjusted population based on 2 of 3 dose reduction criteria in the ARISTOTLE study.

Although treatment with apixaban does not require routine monitoring of exposure, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery.

Clinical efficacy and safety

Prevention of VTE (VTEp): elective hip or knee replacement surgery

The apixaban clinical program was designed to demonstrate the efficacy and safety of apixaban for the prevention of 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/m^2, and 415 patients (203 in the apixaban group) with moderate renal impairment.

The ADVANCE-3 study included 5,407 patients undergoing elective hip replacement, and the ADVANCE-2 study included 3,057 patients undergoing elective knee replacement. 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.

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 DVT, non-fatal PE, and VTE-related death, compared to enoxaparin in both elective hip or knee replacement surgery (see Table 4).

Table 4: Efficacy Results from Pivotal phase III Studies

Study	ADVANCE-3 (hip)			ADVANCE-2 (knee)		
Study treatment Dose Duration of treatment	Apixaban 2.5 mg po twice daily 35 ± 3 d	Enoxaparin 40 mg sc once daily 35 ± 3 d	p-value	Apixaban 2.5 mg po twice daily 12 ± 2 d	Enoxaparin 40 mg sc once daily 12 ± 2 d	p-value
Total VTE/all-cause death						
Number of events/subjects Event Rate	27/1949 1.39%	74/1917 3.86%	<0.0001	147/976 15.06%	243/997 24.37%	<0.0001
Relative Risk 95% CI	0.36 (0.22, 0.54)			0.62 (0.51, 0.74)		
Major VTE						
Number of events/subjects Event Rate	10/2199 0.45%	25/2195 1.14%	0.0107	13/1195 1.09%	26/1199 2.17%	0.0373
Relative Risk 95% CI	0.40 (0.15, 0.80)			0.50 (0.26, 0.97)		

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 5). All the bleeding criteria included surgical site bleeding.

Table 5: Bleeding Results from Pivotal phase III Studies*

	ADVANCE-3		ADVANCE-2	
	Apixaban 2.5 mg po twice daily35 ± 3 d	Enoxaparin 40 mg sc once daily 35 ± 3 d	Apixaban 2.5 mg po twice daily 12 ± 2 d	Enoxaparin 40 mg sc once daily 12 ± 2 d
All treated	n = 2673	n = 2659	n = 1501	n = 1508
Treatment Period[1]				
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%)
Post-surgery treatment period [2]				
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

[1] Includes events occurring after first dose of enoxaparin (pre-surgery)

[2] Includes events occurring after first dose of apixaban (post-surgery)

The overall incidences of adverse reactions of bleeding, anaemia and abnormalities of transaminases (e.g., ALT levels) were numerically lower in patients on apixaban compared to enoxaparin in the phase II and phase III studies in elective hip and knee replacement surgery.

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 number of PE.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)
A total of 23,799 patients were randomised in the clinical program (ARISTOTLE: apixaban versus warfarin, AVERROES: apixaban versus ASA) including 11,927 randomised to apixaban. The program was designed to demonstrate the efficacy and safety of apixaban for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) and one or more additional risk factors, such as:

- prior stroke or transient ischaemic attack (TIA)
- age ≥ 75 years
- hypertension
- diabetes mellitus
- symptomatic heart failure (NYHA Class ≥ II)

ARISTOTLE STUDY
In the ARISTOTLE study a total of 18,201 patients were randomised to double-blind treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [4.7%], see section 4.2) or warfarin (target INR range 2.0-3.0), patients were exposed to study drug for a mean of 20 months. The mean age was 69.1 years, the mean $CHADS_2$ score was 2.1 and 18.9 % of patients had prior stroke or TIA.
In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic or ischaemic) and systemic embolism (see Table 6) compared with warfarin.

Table 6: 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
Stroke				
Ischaemic or unspecified	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)	

For patients randomised to warfarin, the median percentage of time in therapeutic range (TTR) (INR 2-3) was 66%.
Apixaban showed a reduction of stroke and systemic embolism compared to warfarin across the different levels of center TTR; within the highest quartile of TTR according to center, the hazard ratio for apixaban vs warfarin was 0.73 (95% CI, 0.38, 1.40).

Key secondary endpoints of major bleeding and all cause death were tested in a pre-specified hierarchical testing strategy to control the overall type 1 error in the trial. Statistically significant superiority was also achieved in the key secondary endpoints of both major bleeding and all-cause

death (see Table 7). With improving monitoring of INR the observed benefits of apixaban compared to warfarin regarding all cause death diminish.

Table 7: Secondary Endpoints 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**
Bleeding Outcomes				
Major*	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	< 0.0001
Fatal	10 (0.06)	37 (0.24)		
Intracranial	52 (0.33)	122 (0.80)		
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
Other Endpoints				
All-cause death	603 (3.52)	669 (3.94)	0.89 (0.80, 1.00)	0.0465
Myocardial infarction	90 (0.53)	102 (0.61)	0.88 (0.66, 1.17)	

*Major bleeding defined per International Society on Thrombosis and Haemostasis (ISTH) criteria.

The overall discontinuation rate due to adverse reactions was 1.8% for apixaban and 2.6% for warfarin in the ARISTOTLE study.

The efficacy results for prespecified subgroups, including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the primary efficacy results for the overall population studied in the trial.

The incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) was 0.76%/year with apixaban and 0.86%/year with warfarin.

The major bleeding results for prespecified subgroups including $CHADS_2$ score, age, body weight, gender, status of renal function, prior stroke or TIA and diabetes were consistent with the results for the overall population studied in the trial.

AVERROES STUDY

In the AVERROES study a total of 5,598 patients considered to be unsuitable for VKA by the investigators were randomised to treatment with apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients [6.4%], see section 4.2) or ASA. ASA was given at a once daily dose of 81 mg (64%), 162 (26.9%), 243 (2.1%), or 324 mg (6.6%) at the discretion of the investigator. Patients were exposed to study drug for a mean of 14 months. The mean age was 69.9 years, the mean $CHADS_2$ score was 2.0 and 13.6% of patients had prior stroke or TIA.

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%).

AVERROES was stopped early based on a recommendation by the independent Data Monitoring Committee due to clear evidence of reduction of stroke and systemic embolism with an acceptable safety profile.
The overall discontinuation rate due to adverse reactions was 1.5% for apixaban and 1.3% for ASA in the AVERROES study.

In the study, apixaban achieved statistically significant superiority in the primary endpoint of prevention of stroke (haemorrhagic, ischaemic or unspecified) or systemic embolism (see Table 8) compared to ASA.

Table 8: 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 unspecified	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

* Assessed by sequential testing strategy designed to control the overall type I error in the trial.
† Secondary endpoint.

There was no statistically significant difference in the incidence of major bleeding between apixaban and ASA (see Table 9).

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, n	5 (0.16)	5 (0.16)		
Intracranial, n	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

*Major bleeding defined per International Society on Thrombosis ad Haemostasis (ISTH) criteria.
† Clinically Relevant Non-Major

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)
The clinical program (AMPLIFY: apixaban versus enoxaparin/warfarin, AMPLIFY-EXT: apixaban versus placebo) was designed to demonstrate the efficacy and safety of apixaban for the treatment of DVT and/or PE (AMPLIFY), and extended therapy for the prevention of recurrent DVT and/or PE following 6 to 12 months of anticoagulant treatment for DVT and/or PE (AMPLIFY-EXT). Both studies were randomised, parallel-group, double-blind, multinational trials in patients with symptomatic proximal DVT or symptomatic PE. All the key safety and efficacy endpoints were adjudicated by an independent blinded committee.

AMPLIFY STUDY
In the AMPLIFY study a total of 5,395 patients were randomised to treatment with apixaban 10 mg twice daily orally for 7 days followed by apixaban 5 mg twice daily orally for 6 months, or enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR≥ 2) and warfarin (target INR range 2.0-3.0) orally for 6 months.

The mean age was 56.9 years and 89.8% of randomised patients had unprovoked VTE events.

For patients randomised to warfarin, the mean percentage of time in therapeutic range (INR 2.0-3.0) was 60.9. Apixaban showed a reduction in recurrent symptomatic VTE or VTE- related death across the different levels of center TTR; within the highest quartile of TTR according to center, the relative risk for apixaban vs enoxaparin/warfarin was 0.79 (95% CI, 0.39, 1.61).

In the study, apixaban was shown to be non-inferior to enoxaparin/warfarin in the combined primary endpoint of adjudicated recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death (see Table 10).

Table 10: Efficacy Results in the AMPLIFY Study

	Apixaban N=2609 n (%)	**Enoxaparin/Warfarin N=2635 n (%)**	**Relative Risk (95% CI)**
VTE or VTE-related death	59 (2.3)	71 (2.7)	0.84 (0.60, 1.18)*
DVT	20 (0.7)	33 (1.2)	
PE	27 (1.0)	23 (0.9)	
VTE-related death	12 (0.4)	15 (0.6)	
VTE or all-cause death	84 (3.2)	104 (4.0)	0.82 (0.61, 1.08)
VTE or CV-related death	61 (2.3)	77 (2.9)	0.80 (0.57, 1.11)
VTE, VTE-related death, or major bleeding	73 (2.8)	118 (4.5)	0.62 (0.47, 0.83)

* Noninferior compared to enoxaparin/warfarin (p-value <0.0001)

Apixaban efficacy in initial treatment of VTE was consistent between patients who were treated for a PE [Relative Risk 0.9; 95% CI (0.5, 1.6)] or DVT [Relative Risk 0.8; 95% CI (0.5, 1.3)]. Efficacy across subgroups, including age, gender, body mass index (BMI), renal function, extent of index PE, location of DVT thrombus, and prior parenteral heparin use was generally consistent.

The primary safety endpoint was major bleeding. In the study, apixaban was statistically superior to enoxaparin/warfarin in the primary safety endpoint [Relative Risk 0.31, 95% confidence interval (0.17, 0.55), P-value <0.0001] (see Table 11).

Table 11: Bleeding Results in the AMPLIFY Study

	Apixaban N=2676 n (%)	**Enoxaparin/ Warfarin N=2689 n (%)**	**Relative Risk (95% CI)**
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55)
Major + CRNM	115 (4.3)	261 (9.7)	0.44 (0.36, 0.55)
Minor	313 (11.7)	505 (18.8)	0.62 (0.54, 0.70)
All	402 (15.0)	676 (25.1)	0.59 (0.53, 0.66)

The adjudicated major bleeding and CRNM bleeding at any anatomical site were generally lower in the apixaban group as compared to the enoxaparin/warfarin group. Adjudicated ISTH major gastrointestinal bleeding occurred in 6 (0.2%) apixaban-treated patients and 17 (0.6%) enoxaparin/warfarin-treated patients.

AMPLIFY-EXT STUDY

In the AMPLIFY-EXT study a total of 2,482 patients were randomised to treatment with apixaban 2.5 mg twice daily orally, apixaban 5 mg twice daily orally, or placebo for 12 months after completing 6 to

12 months of initial anticoagulant treatment. Of these, 836 patients (33.7%) participated in the AMPLIFY study prior to enrollment in the AMPLIFY-EXT study.

The mean age was 56.7 years and 91.7% of randomised patients had unprovoked VTE events.

In the study, both doses of apixaban were statistically superior to placebo in the primary endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death (see Table 12).

Table 12: Efficacy Results in the AMPLIFY-EXT Study

	Apixaban	**Apixaban**	**Placebo**	**Relative Risk (95% CI)**	
	2.5 mg (N=840)	**5.0 mg (N=813)**	**(N=829)**	**Apix 2.5 mg vs. Placebo**	**Apix 5.0 mg vs. Placebo**
	n (%)				
Recurrent VTE or all-cause death	19 (2.3)	14 (1.7)	77 (9.3)	0.24 (0.15, 0.40)¥	0.19 (0.11, 0.33)¥
DVT*	6 (0.7)	7 (0.9)	53 (6.4)		
PE*	7 (0.8)	4 (0.5)	13 (1.6)		
All-cause death	6 (0.7)	3 (0.4)	11 (1.3)		
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11, 0.33)	0.20 (0.11, 0.34)
Recurrent VTE or CV-related death	14 (1.7)	14 (1.7)	76 (9.2)	0.18 (0.10, 0.32)	0.19 (0.11, 0.33)
Nonfatal DVT†	6 (0.7)	8 (1.0)	53 (6.4)	0.11 (0.05, 0.26)	0.15 (0.07, 0.32)
Nonfatal PE†	8 (1.0)	4 (0.5)	15 (1.8)	0.51 (0.22, 1.21)	0.27 (0.09, 0.80)
VTE-related death	2 (0.2)	3 (0.4)	7 (0.8)	0.28 (0.06, 1.37)	0.45 (0.12, 1.71)

¥ p-value <0.0001

* For patients with more than one event contributing to the composite endpoint, only the first event was reported (eg, if a subject experienced both a DVT and then a PE, only the DVT was reported)

† Individual subjects could experience more than one event and be represented in both classifications

Apixaban efficacy for prevention of a recurrence of a VTE was maintained across subgroups, including age, gender, BMI, and renal function.

The primary safety endpoint was major bleeding during the treatment period. In the study, the incidence in major bleeding for both apixaban doses was not statistically different from placebo. There was no statistically significant difference in the incidence of major + CRNM, minor, and all bleeding between the apixaban 2.5 mg twice daily and placebo treatment groups (see Table 13).

Table 13: Bleeding Results in the AMPLIFY-EXT Study

	Apixaban	**Apixaban**	**Placebo**	**Relative Risk (95% CI)**	
	2.5 mg (N=840)	**5.0 mg** (N=811)	(N=826)	**Apix 2.5 mg** vs. Placebo	**Apix 5.0 mg** vs. Placebo

	Apixaban	Apixaban	Placebo	Relative Risk (95% CI)	
		n (%)			
Major	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09, 2.64)	0.25 (0.03, 2.24)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)	1.20 (0.69, 2.10)	1.62 (0.96, 2.73)
Minor	75 (8.9)	98 (12.1)	58 (7.0)	1.26 (0.91, 1.75)	1.70 (1.25, 2.31)
All	94 (11.2)	121 (14.9)	74 (9.0)	1.24 (0.93, 1.65)	1.65 (1.26, 2.16)

Adjudicated ISTH major gastrointestinal bleeding occurred in 1 (0.1%) apixaban-treated patient at the 5 mg twice daily dose, no patients at the 2.5 mg twice daily dose, and 1 (0.1%) placebo-treated patient.

Paediatric Population

The European Medicines Agency has deferred the obligation to submit the results of studies with ELIQUIS in one or more subsets of the paediatric population in venous and arterial embolism and thrombosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 ≥ 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 ~20% CV and ~30% CV, respectively.

Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was comparable to exposure after oral administration of 2 whole 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets with 30 g of apple puree, the C_{max} and AUC were 21% and 16% lower, respectively, when compared to administration of 2 whole 5 mg tablets. The reduction in exposure is not considered clinically relevant.

Following administration of a crushed 5 mg apixaban tablet suspended in 60 mL of D5W and delivered via a nasogastric tube, exposure was similar to exposure seen in other clinical trials involving healthy subjects receiving a single oral 5 mg apixaban tablet dose.

Given the predictable, dose-proportional pharmacokinetic profile of apixaban, the bioavailability results from the conducted studies are applicable to lower apixaban doses.

Distribution

Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 litres.

Biotransformation 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 transport proteins, P-gp and breast cancer resistance protein (BCRP).

Renal impairment
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.

In subjects with end-stage renal disease (ESRD), the AUC of apixaban was increased by 36% when a single dose of apixaban 5 mg was administered immediately after haemodialysis, compared to that seen in subjects with normal renal function. Haemodialysis, started two hours after administration of a single dose of apixaban 5 mg, decreased apixaban AUC by 14% in these ESRD subjects, corresponding to an apixaban dialysis clearance of 18 mL/min. Therefore, haemodialysis is unlikely to be an effective means of managing apixaban overdose.

Hepatic impairment
In a study comparing 8 subjects with mild hepatic impairment, Child-Pugh A score 5 (n = 6) and score 6 (n = 2), and 8 subjects with moderate hepatic impairment. Child-Pugh B score 7 (n = 6) and score 8 (n = 2), to 16 healthy control subjects, the single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in subjects with hepatic impairment. Changes in anti-Factor Xa activity and INR were comparable between subjects with mild to moderate hepatic impairment and healthy subjects.

Elderly
Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32% higher and no difference in C_{max}.

Gender
Exposure to apixaban was approximately 18% higher in females than in males.

Ethnic origin and race
The results across phase 1 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 generally consistent with the phase 1 results.

Body weight
Compared to 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.

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-Factor Xa activity was best described by a linear model. The PK/PD relationship observed in patients was consistent with that established in healthy subjects.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-foetal development and juvenile toxicity.

The major observed effects in the repeated dose toxicity studies were those related to the pharmacodynamic action of apixaban on blood coagulation parameters. In the toxicity studies little to no increase of bleeding tendency was found. However, since this may be due to a lower sensitivity of the non-clinical species compared to humans, this result should be interpreted with caution when extrapolating to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Anhydrous lactose
Microcrystalline cellulose
Croscarmellose sodium
Sodium lauryl sulfate
Magnesium stearate

Film coat:
Hypromellose
Lactose monohydrateTitanium dioxide
Triacetin
Iron oxide Yellow (2.5mg film-coated tablets)
Iron oxide Red (5mg film-coated tablets)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 30^0C.

6.5 Nature and contents of container

Eliquis 2.5 mg film-coated tabltes

Alu-PVC/PVdC blisters. Cartons of 10, 20 and 60 film-coated tablets.

Alu-PVC/PVdC perforated unit dose blisters of 60 x 1 and 100 x 1 film-coated tablets.

Eliquis 5 mg film-coated tabltes

Alu-PVC/PVdC blisters. Cartons of 14, 20, 56 and 60 film-coated tablets.

Alu-PVC/PVdC perforated unit dose blisters of 100x1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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