

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use ELIQUIS safely and effectively. See full prescribing information for ELIQUIS.

ELIQUIS® (apixaban) tablets for oral use  
Initial U.S. Approval: 2012

**WARNING: (A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE**

**(B) SPINAL/EPIDURAL HEMATOMA**

See full prescribing information for complete boxed warning.

**(A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE:** Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered. (2.5, 5.1)

**(B) SPINAL/EPIDURAL HEMATOMA:** ELIQUIS use in patients undergoing spinal epidural anesthesia or spinal puncture increases the risk of epidural or spinal hematoma which may cause long-term or permanent paralysis. Monitor patients frequently for signs and symptoms of neurologic impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated. (5.3)

**RECENT MAJOR CHANGES**

Boxed Warning	03/2014
Indications and Usage (1.2)	03/2014
Dosage and Administration (2.1)	03/2014
Dosage and Administration (2.8)	03/2014
Warnings and Precautions (5.3)	03/2014

**INDICATIONS AND USAGE**

ELIQUIS is a factor Xa inhibitor anticoagulant indicated:

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. (1.1)
- for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery. (1.2)

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**(B) SPINAL/EPIDURAL HEMATOMA**

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**DOSAGE AND ADMINISTRATION**

- Reduction in risk of stroke and systemic embolism in nonvalvular atrial fibrillation:
  - The recommended dose is 5 mg orally twice daily. (2.1)
  - In patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. (2.2)
- Prophylaxis of DVT following hip or knee replacement surgery:
  - The recommended dose is 2.5 mg orally twice daily. (2.1)

**DOSAGE FORMS AND STRENGTHS**

- Tablets: 2.5 mg and 5 mg (3)

**CONTRAINDICATIONS**

- Active pathological bleeding (4)
- Severe hypersensitivity to ELIQUIS (4)

**WARNINGS AND PRECAUTIONS**

- ELIQUIS can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.2)
- Prosthetic heart valves: ELIQUIS use not recommended. (5.4)

**ADVERSE REACTIONS**

Most common adverse reactions (>1%) are related to bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

- Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of apixaban: Reduce ELIQUIS dose to 2.5 mg or avoid concomitant use. (2.2, 7.1, 12.3)
- Simultaneous use of strong dual inducers of CYP3A4 and P-gp reduces blood levels of apixaban: Avoid concomitant use. (7.2, 12.3)

**USE IN SPECIFIC POPULATIONS**

- Nursing Mothers:* Discontinue drug or discontinue nursing. (8.3)
- Pregnancy:* Not recommended. (8.1)
- Severe Hepatic Impairment:* Not recommended. (12.2)

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Revised: 03/2014

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## FULL PRESCRIBING INFORMATION

### **WARNING: (A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE**

#### **(B) SPINAL/EPIDURAL HEMATOMA**

### **(A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE**

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered [*see Dosage and Administration (2.5) and Warnings and Precautions (5.1)*].

#### **(B) SPINAL/EPIDURAL HEMATOMA**

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins, heparinoids, or Factor Xa inhibitors for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Monitor patients for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary.

Consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis [*see Warnings and Precautions (5.3)*].

## 1 INDICATIONS AND USAGE

### 1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

ELIQUIS<sup>®</sup> (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

### 1.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dose

#### *Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation*

The recommended dose of ELIQUIS for most patients is 5 mg taken orally twice daily.

#### *Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery*

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

- In patients undergoing hip replacement surgery, the recommended duration of treatment is 35 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.

### 2.2 Dosage Adjustments

*In patients with nonvalvular atrial fibrillation:* The recommended dose of ELIQUIS is 2.5 mg twice daily in patients with any 2 of the following characteristics:

- age  $\geq$ 80 years

- body weight  $\leq 60$  kg
- serum creatinine  $\geq 1.5$  mg/dL

*Coadministration with CYP3A4 and P-gp inhibitors:* For patients receiving ELIQUIS 5 mg twice daily when ELIQUIS is coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin), the recommended dose is 2.5 mg twice daily [see *Clinical Pharmacology (12.3)*].

In patients already taking 2.5 mg twice daily, coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp should be avoided.

### **2.3 Missed Dose**

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

### **2.4 Temporary Interruption for Surgery and Other Interventions**

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

### **2.5 Converting from or to ELIQUIS**

*Switching from warfarin to ELIQUIS:* Warfarin should be discontinued and ELIQUIS started when the international normalized ratio (INR) is below 2.0.

*Switching from ELIQUIS to warfarin:* ELIQUIS affects INR, so that initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. If continuous anticoagulation is necessary, discontinue ELIQUIS and begin both a parenteral anticoagulant and warfarin at the time the next dose of ELIQUIS would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

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

## **2.6 Hepatic Impairment**

No dose adjustment is required in patients with mild hepatic impairment.

Because patients with moderate hepatic impairment may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided [see *Clinical Pharmacology (12.2)*].

ELIQUIS is not recommended in patients with severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

## **2.7 Renal Impairment**

The dosing adjustment for moderate renal impairment is described above [see *Dosage and Administration (2.2)*]. The recommended dose for nonvalvular atrial fibrillation patients with end-stage renal disease (ESRD) maintained on hemodialysis is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if one of the following patient characteristics (age  $\geq$ 80 years or body weight  $\leq$ 60 kg) is present [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

## **2.8 Administration Options**

For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS tablets may be crushed and suspended in 60 mL D5W and immediately delivered through a nasogastric tube (NGT) [see *Clinical Pharmacology (12.3)*]. Information regarding the administration of crushed and suspended ELIQUIS tablets swallowed by mouth is not available.

## **3 DOSAGE FORMS AND STRENGTHS**

- 2.5 mg, yellow, round, biconvex, film-coated tablets with “893” debossed on one side and “2½” on the other side.
- 5 mg, pink, oval-shaped, biconvex, film-coated tablets with “894” debossed on one side and “5” on the other side.

## 4 CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding [*see Warnings and Precautions (5.2) and Adverse Reactions (6.1)*]
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) [*see Adverse Reactions (6.1)*]

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Increased Risk of Stroke with Discontinuation of ELIQUIS in Patients with Nonvalvular Atrial Fibrillation

Discontinuing ELIQUIS in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in patients with nonvalvular atrial fibrillation [*see Clinical Studies (14.1)*]. If ELIQUIS must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant [*see Dosage and Administration (2.5)*].

### 5.2 Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding [*see Dosage and Administration (2.2) and Adverse Reactions (6.1)*].

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) [*see Drug Interactions (7.3)*].

Patients should be made aware of signs and symptoms of blood loss and instructed to report them immediately or go to an emergency room. ELIQUIS should be discontinued in patients with active pathological hemorrhage.

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose, i.e., for about two half-lives. A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure [*see Clinical Pharmacology (12.3)*]. Protamine sulfate

and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration [*see Overdosage (10)*].

### **5.3 Spinal/Epidural Anesthesia or Puncture**

When neuraxial anesthesia (spinal/epidural anesthesia) 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 hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

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.

### **5.4 Patients with Prosthetic Heart Valves**

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

## 6 ADVERSE REACTIONS

The most serious adverse reactions reported with ELIQUIS were related to bleeding [*see Warnings and Precautions (5.2)*].

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

#### *Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation*

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies [*see Clinical Studies (14)*], including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was  $\geq 12$  months for 9375 patients and  $\geq 24$  months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks ( $>15,000$  patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks ( $>3000$  patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

#### **Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES**

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per year) in ARISTOTLE and AVERROES.

*Major bleeding* was defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in hemoglobin of 2 g/dL or more; a transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or bleeding that was fatal. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

**Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE**

	<b>ELIQUIS N=9088 n (%/year)</b>	<b>Warfarin N=9052 n (%/year)</b>	<b>Hazard Ratio (95% CI*)</b>	<b>P-value</b>
Major <sup>†</sup>	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Gastrointestinal (GI) <sup>‡</sup>	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Intracranial	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Intraocular <sup>§</sup>	32 (0.21)	22 (0.14)	1.42 (0.83, 2.45)	-
Fatal <sup>¶</sup>	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
CRNM <sup>**</sup>	318 (2.08)	444 (3.00)	0.70 (0.60, 0.80)	<0.0001

\* Confidence interval.

<sup>†</sup> International Society on Thrombosis and Hemostasis (ISTH) major bleed assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.

<sup>‡</sup> GI bleed includes upper GI, lower GI, and rectal bleeding.

<sup>§</sup> Intraocular bleed is within the corpus of the eye (a conjunctival bleed is not an intraocular bleed).

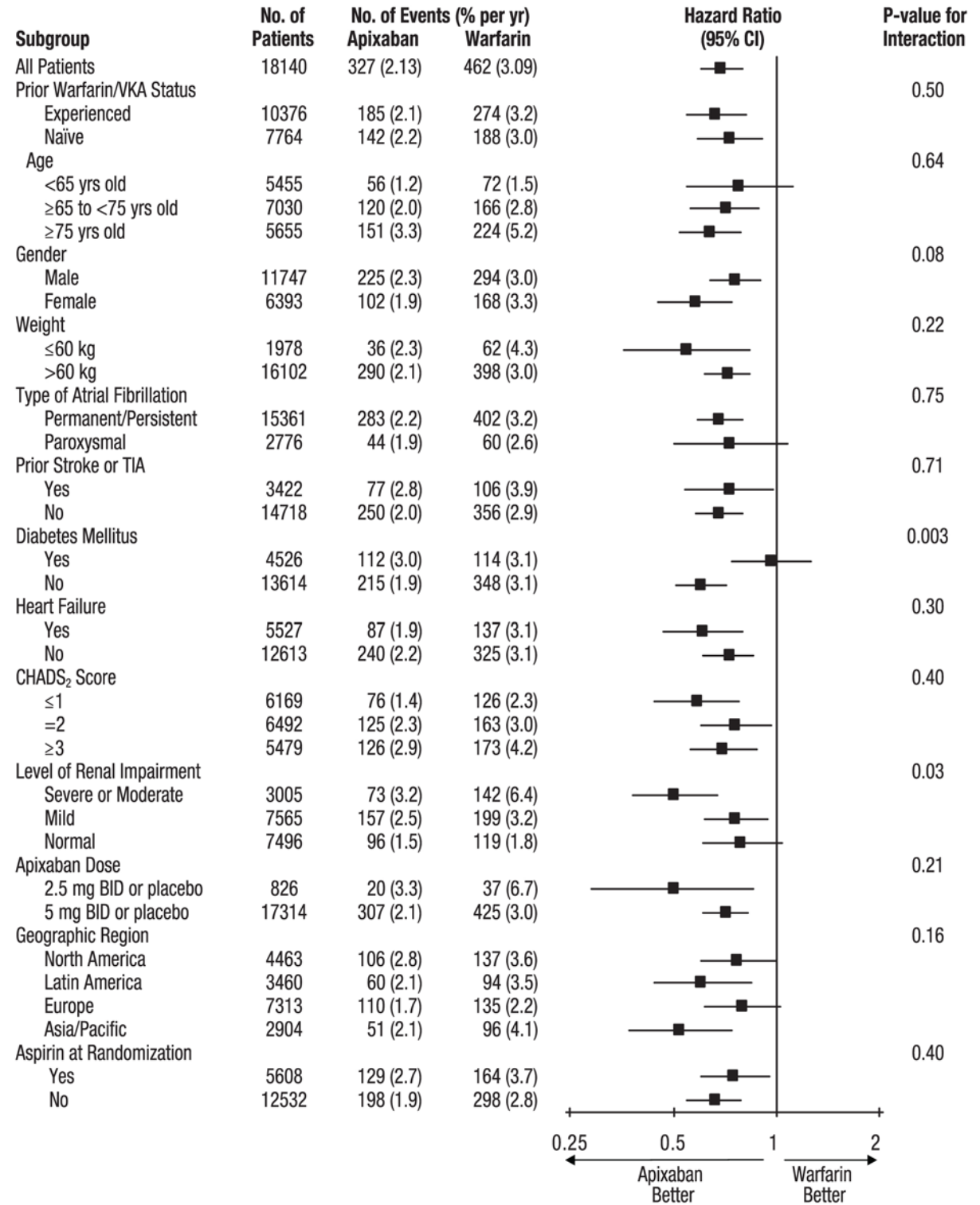
<sup>¶</sup> Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal extracranial bleeds and fatal hemorrhagic stroke.

<sup>\*\*</sup> CRNM = clinically relevant nonmajor bleeding.

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

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, CHADS<sub>2</sub> score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, ELIQUIS dose, type of atrial fibrillation (AF), and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

**Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study**



**Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES**

	<b>ELIQUIS N=2798 n (%/year)</b>	<b>Aspirin N=2780 n (%/year)</b>	<b>Hazard Ratio (95% CI)</b>	<b>P-value</b>
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

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

### Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

### *Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery*

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

**Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery**

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%) <sup>†</sup>	18 (0.68%)	9 (0.60%) <sup>‡</sup>	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site <sup>§</sup>	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM <sup>¶</sup>	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

\* All bleeding criteria included surgical site bleeding.

<sup>†</sup> Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

<sup>‡</sup> Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

<sup>§</sup> Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.

<sup>¶</sup> CRNM = clinically relevant nonmajor.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

**Table 4: Adverse Reactions Occurring in  $\geq 1\%$  of Patients in Either Group Undergoing Hip or Knee Replacement Surgery**

	<b>ELIQUIS, n (%)</b> <b>2.5 mg po bid</b> <b>N=5924</b>	<b>Enoxaparin, n (%)</b> <b>40 mg sc qd or</b> <b>30 mg sc q12h</b> <b>N=5904</b>
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of  $\geq 0.1\%$  to  $< 1\%$ :

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

*Vascular disorders:* hypotension (including procedural hypotension)

*Respiratory, thoracic, and mediastinal disorders:* epistaxis

*Gastrointestinal disorders:* gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

*Hepatobiliary disorders:* liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

*Renal and urinary disorders:* hematuria (including respective laboratory parameters)

*Injury, poisoning, and procedural complications:* wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

## **7 DRUG INTERACTIONS**

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke.

### **7.1 Strong Dual Inhibitors of CYP3A4 and P-gp**

For patients receiving 5 mg twice daily, the dose of ELIQUIS should be decreased to 2.5 mg twice daily when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

In patients already taking ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

### **7.2 Strong Dual Inducers of CYP3A4 and P-gp**

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban [*see Clinical Pharmacology (12.3)*].

### **7.3 Anticoagulants and Antiplatelet Agents**

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of

ISTH major bleeding was 2.77% per year with apixaban versus 0.62% per year with placebo in patients receiving single antiplatelet therapy and was 5.91% per year with apixaban versus 2.50% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### *Pregnancy Category B*

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

### **8.2 Labor and Delivery**

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting [*see Warnings and Precautions (5.2)*].

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during

gestation, occurred at apixaban doses of  $\geq 25$  mg/kg, a dose corresponding to  $\geq 1.3$  times the human exposure.

### **8.3 Nursing Mothers**

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS therapy, taking into account the importance of the drug to the mother.

### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

### **8.5 Geriatric Use**

Of the total subjects in the ARISTOTLE and AVERROES clinical studies,  $>69\%$  were 65 and older, and  $>31\%$  were 75 and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 and older, while 16% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

### **8.6 End-Stage Renal Disease Patients Maintained with Hemodialysis**

Patients with ESRD with or without hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendation for patients with nonvalvular atrial fibrillation is based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis. The recommended dose for ESRD patients maintained with hemodialysis is 5 mg orally twice daily. For ESRD patients maintained with hemodialysis with one of the following patient characteristics, age  $\geq 80$  years or body weight  $\leq 60$  kg, reduce dose to 2.5 mg twice daily [*see Dosage and Administration (2.7) and Clinical Pharmacology (12.2, 12.3)*].

## 10 OVERDOSAGE

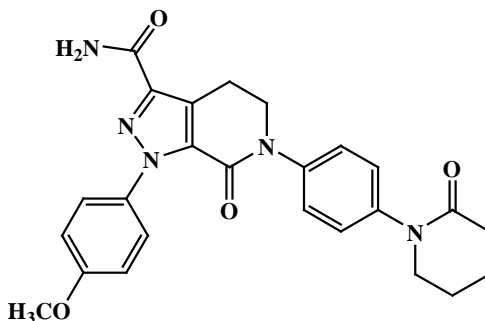
There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding [*see Warnings and Precautions (5.2)*].

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 for 7 days or 50 mg once daily 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. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

## 11 DESCRIPTION

ELIQUIS (apixaban), a factor Xa (FXa) inhibitor, is chemically described as 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide. Its molecular formula is  $C_{25}H_{25}N_5O_4$ , which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



Apixaban is a white to pale-yellow powder. At physiological pH (1.2–6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL.

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Apixaban is a selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development.

### 12.2 Pharmacodynamics

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, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban.

The Rotachrom<sup>®</sup> Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program. A concentration-dependent increase in anti-FXa activity was observed in the dose range tested and was similar in healthy subjects and patients with AF.

This test is not recommended for assessing the anticoagulant effect of apixaban.

#### *Pharmacodynamic Drug Interaction Studies*

Pharmacodynamic drug interaction studies with aspirin, clopidogrel, aspirin and clopidogrel, prasugrel, enoxaparin, and naproxen were conducted. No pharmacodynamic interactions were observed with aspirin, clopidogrel, or prasugrel [*see Warnings and Precautions (5.2)*]. A 50% to 60% increase in anti-FXa activity was observed when apixaban was coadministered with enoxaparin or naproxen.

#### *Specific Populations*

*Renal impairment:* Anti-FXa activity adjusted for exposure to apixaban was similar across renal function categories.

*Hepatic impairment:* Changes in anti-FXa activity were similar in patients with mild-to-moderate hepatic impairment and healthy subjects. However, in patients with moderate hepatic impairment, there is no clear understanding of the impact of this degree of hepatic function impairment on the coagulation cascade and its relationship to efficacy and bleeding. Patients with severe hepatic impairment were not studied.

#### *Cardiac Electrophysiology*

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

### **12.3 Pharmacokinetics**

Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg.

#### *Absorption*

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg of ELIQUIS. Food does not affect the bioavailability of apixaban. Maximum concentrations ( $C_{max}$ ) of apixaban appear 3 to 4 hours after oral administration of ELIQUIS. At doses  $\geq 25$  mg, apixaban displays dissolution-limited absorption with decreased bioavailability. Following administration of a crushed 5 mg ELIQUIS tablet that was suspended in 60 mL D5W and delivered through a nasogastric tube (NGT), exposure was similar to that seen in other clinical trials involving healthy volunteers receiving a single oral 5 mg tablet dose.

#### *Distribution*

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

#### *Metabolism*

Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation.

Unchanged apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.

### *Elimination*

Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces.

Apixaban has a total clearance of approximately 3.3 L/hour and an apparent half-life of approximately 12 hours following oral administration.

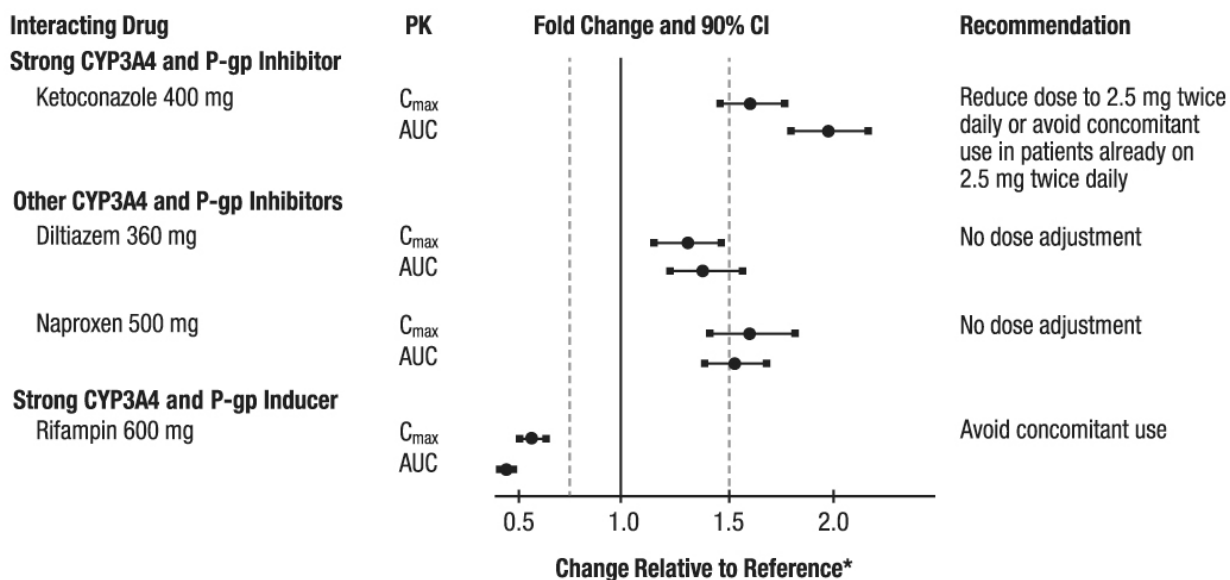
Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

### *Drug Interaction Studies*

*In vitro* apixaban studies at concentrations significantly greater than therapeutic exposures, no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4/5, or CYP2C19, nor induction effect on the activity of CYP1A2, CYP2B6, or CYP3A4/5 were observed. Therefore, apixaban is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

The effects of coadministered drugs on the pharmacokinetics of apixaban and associated dose recommendations are summarized in Figure 2 [*see also Warnings and Precautions (5.2) and Drug Interactions (7)*].

**Figure 2: Effect of Coadministered Drugs on the Pharmacokinetics of Apixaban**



\* Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations. Dosing recommendations were also informed by clinical considerations [see *Warnings and Precautions (5.2) and Drug Interactions (7)*].

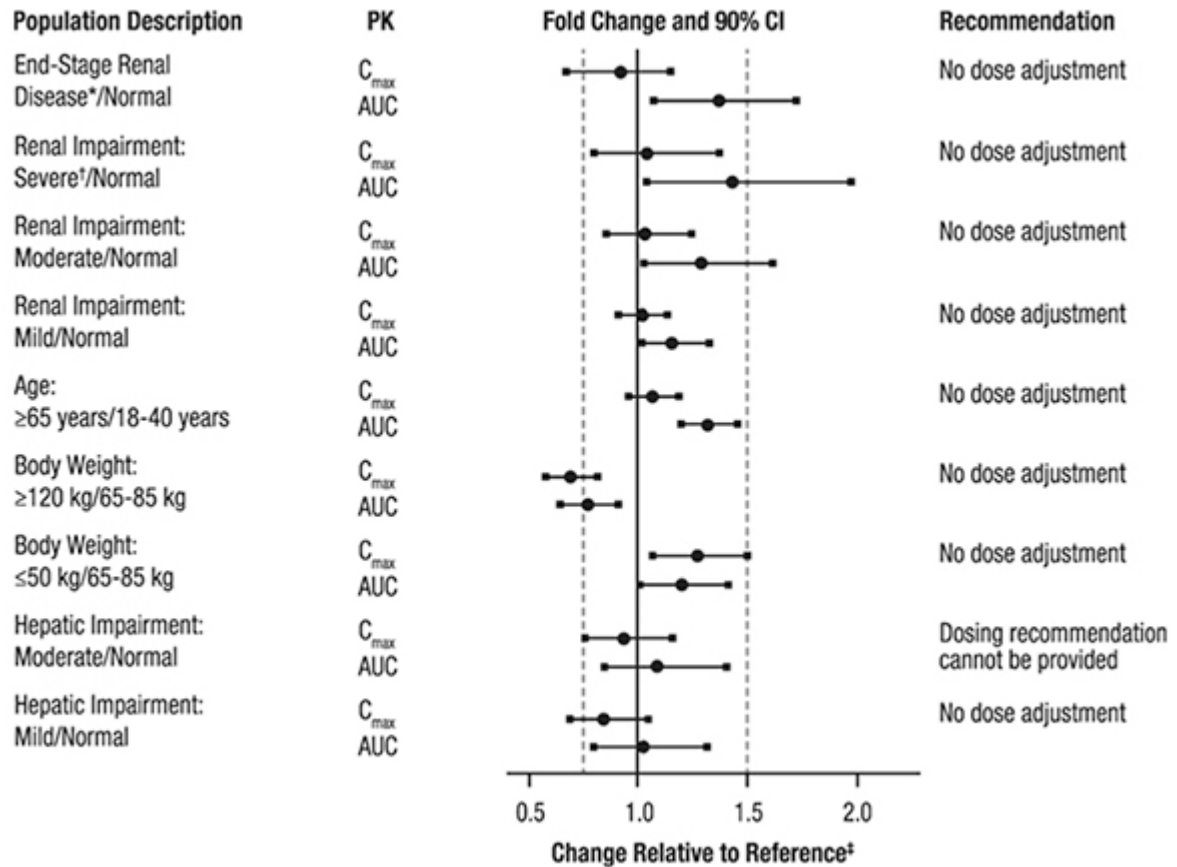
In dedicated studies conducted in healthy subjects, famotidine, atenolol, prasugrel, and enoxaparin did not meaningfully alter the pharmacokinetics of apixaban.

In studies conducted in healthy subjects, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, atenolol, prasugrel, or acetylsalicylic acid.

### *Specific Populations*

The effects of level of renal impairment, age, body weight, and level of hepatic impairment on the pharmacokinetics of apixaban are summarized in Figure 3.

**Figure 3: Effect of Specific Populations on the Pharmacokinetics of Apixaban**



\* ESRD subjects maintained with chronic and stable hemodialysis; reported PK findings are following single dose of apixaban post hemodialysis.  
† Creatinine clearance 15 to 29 mL/min.  
‡ Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations.

A study in healthy subjects comparing the pharmacokinetics in males and females showed no meaningful difference.

The results across pharmacokinetic studies in normal subjects showed no differences in apixaban pharmacokinetics among White/Caucasian, Asian, and Black/African American subjects. No dose adjustment is required based on race/ethnicity.

In subjects with ESRD, a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min started 2 hours after administration of a single 5 mg dose of apixaban, the AUC of apixaban was 17% greater compared to those with

normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min resulting in a 14% decrease in exposure due to hemodialysis compared to off-dialysis period.

Protein binding was similar (92%-94%) between healthy controls and the on-dialysis and off-dialysis periods.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

*Carcinogenesis:* Apixaban was not carcinogenic when administered to mice and rats for up to 2 years. The systemic exposures (AUCs) of unbound apixaban in male and female mice at the highest doses tested (1500 and 3000 mg/kg/day) were 9 and 20 times, respectively, the human exposure of unbound drug at the MRHD of 10 mg/day. Systemic exposures of unbound apixaban in male and female rats at the highest dose tested (600 mg/kg/day) were 2 and 4 times, respectively, the human exposure.

*Mutagenesis:* Apixaban was neither mutagenic in the bacterial reverse mutation (Ames) assay, nor clastogenic in Chinese hamster ovary cells *in vitro*, in a 1-month *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes, or in a rat micronucleus study *in vivo*.

*Impairment of Fertility:* Apixaban had no effect on fertility in male or female rats when given at doses up to 600 mg/kg/day, a dose resulting in exposure levels that are 3 and 4 times, respectively, the human exposure.

Apixaban administered to female rats at doses up to 1000 mg/kg/day from implantation through the end of lactation produced no adverse findings in male offspring (F<sub>1</sub> generation) at doses up to 1000 mg/kg/day, a dose resulting in exposure that is 5 times the human exposure. Adverse effects in the F<sub>1</sub>-generation female offspring were limited to decreased mating and fertility indices at 1000 mg/kg/day.

## 14 CLINICAL STUDIES

### 14.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

#### *ARISTOTLE*

Evidence for the efficacy and safety of ELIQUIS was derived from ARISTOTLE, a multinational, double-blind study in patients with nonvalvular AF comparing the effects of ELIQUIS and warfarin on the risk of stroke and non-central nervous system (CNS) systemic embolism. In ARISTOTLE, patients were randomized to ELIQUIS 5 mg orally twice daily (or 2.5 mg twice daily in subjects with at least 2 of the following characteristics: age  $\geq$ 80 years, body weight  $\leq$ 60 kg, or serum creatinine  $\geq$ 1.5 mg/dL) or to warfarin (targeted to an INR range of 2.0–3.0). Patients had to have one or more of the following additional risk factors for stroke:

- prior stroke or transient ischemic attack (TIA)
- prior systemic embolism
- age  $\geq$ 75 years
- arterial hypertension requiring treatment
- diabetes mellitus
- heart failure  $\geq$ New York Heart Association Class 2
- left ventricular ejection fraction  $\leq$ 40%

The primary objective of ARISTOTLE was to determine whether ELIQUIS 5 mg twice daily (or 2.5 mg twice daily) was effective (noninferior to warfarin) in reducing the risk of stroke (ischemic or hemorrhagic) and systemic embolism. Superiority of ELIQUIS to warfarin was also examined for the primary endpoint (rate of stroke and systemic embolism), major bleeding, and death from any cause.

A total of 18,201 patients were randomized and followed on study treatment for a median of 89 weeks. Forty-three percent of patients were vitamin K antagonist (VKA) “naive,” defined as having received  $\leq$ 30 consecutive days of treatment with warfarin or another VKA before entering the study. The mean age was 69 years and the mean CHADS<sub>2</sub> score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk) was 2.1. The population was 65% male, 83% Caucasian, 14% Asian, and 1% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 19% of patients. Concomitant diseases of patients in this study included hypertension 88%, diabetes 25%, congestive heart failure (or left

ventricular ejection fraction  $\leq 40\%$ ) 35%, and prior myocardial infarction 14%. Patients treated with warfarin in ARISTOTLE had a mean percentage of time in therapeutic range (INR 2.0–3.0) of 62%.

ELIQUIS was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (Table 5 and Figure 4). Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs.

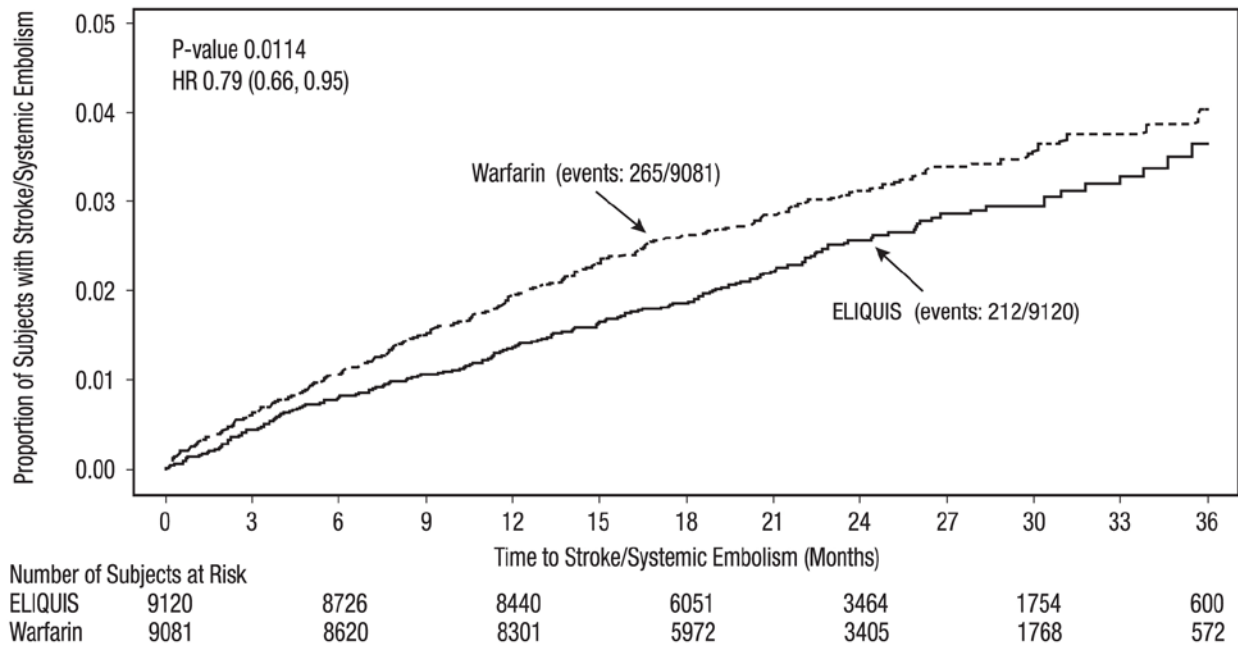
ELIQUIS also showed significantly fewer major bleeds than warfarin [see *Adverse Reactions (6.1)*].

**Table 5: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE (Intent-to-Treat Analysis)**

	<b>ELIQUIS N=9120 n (%/year)</b>	<b>Warfarin N=9081 n (%/year)</b>	<b>Hazard Ratio (95% CI)</b>	<b>P-value</b>
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.01
Stroke	199 (1.19)	250 (1.51)	0.79 (0.65, 0.95)	
Ischemic without hemorrhage	140 (0.83)	136 (0.82)	1.02 (0.81, 1.29)	
Ischemic with hemorrhagic conversion	12 (0.07)	20 (0.12)	0.60 (0.29, 1.23)	
Hemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	
Unknown	14 (0.08)	21 (0.13)	0.65 (0.33, 1.29)	
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	

The primary endpoint was based on the time to first event (one per subject). Component counts are for subjects with any event, not necessarily the first.

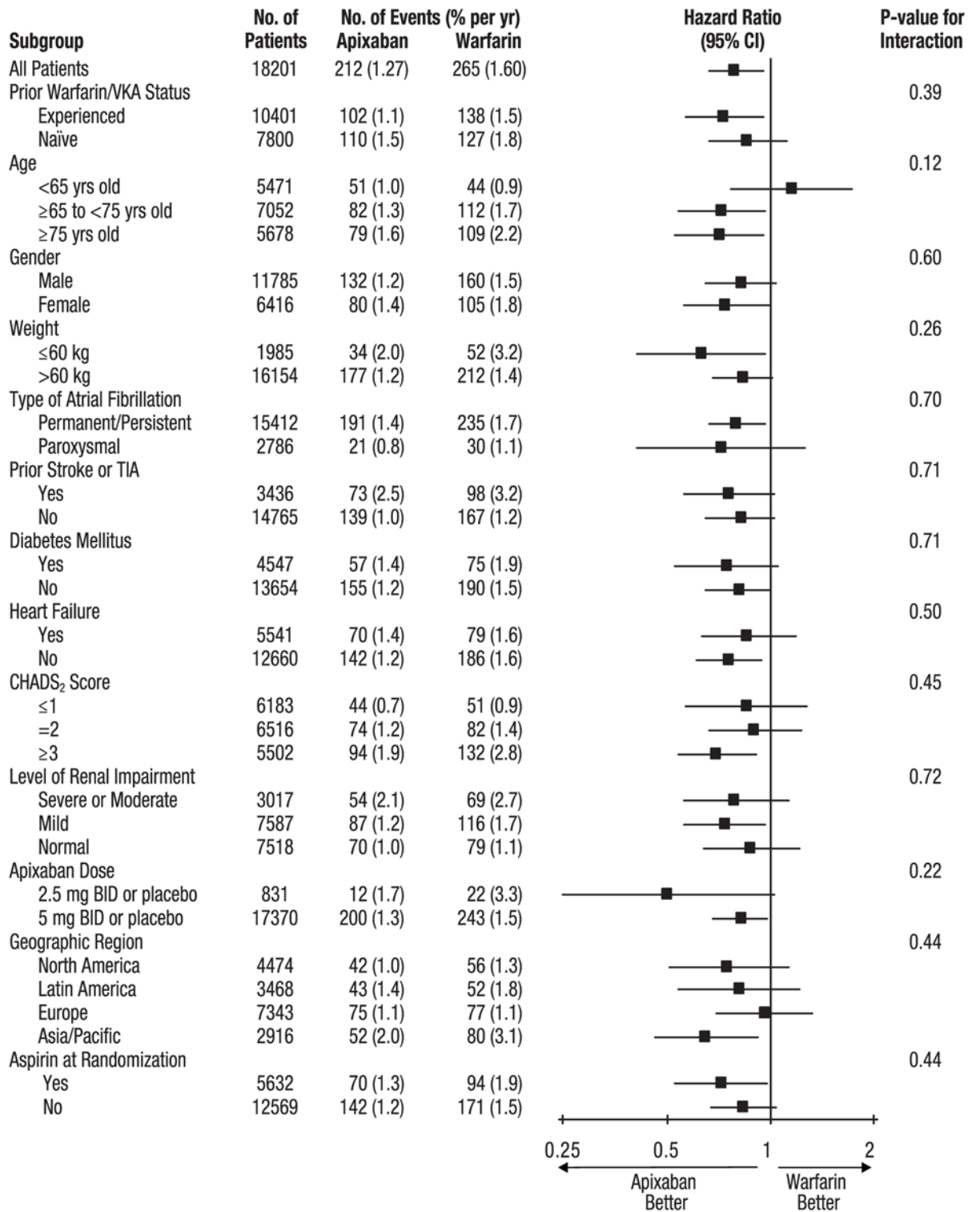
**Figure 4: Kaplan-Meier Estimate of Time to First Stroke or Systemic Embolism in ARISTOTLE (Intent-to-Treat Population)**



All-cause death was assessed using a sequential testing strategy that allowed testing for superiority if effects on earlier endpoints (stroke plus systemic embolus and major bleeding) were demonstrated. ELIQUIS treatment resulted in a significantly lower rate of all-cause death ( $p = 0.046$ ) than did treatment with warfarin, primarily because of a reduction in cardiovascular death, particularly stroke deaths. Non-vascular death rates were similar in the treatment arms.

In ARISTOTLE, the results for the primary efficacy endpoint were generally consistent across most major subgroups including weight, CHADS<sub>2</sub> score (a scale from 0 to 6 used to predict risk of stroke in patients with AF, with higher scores predicting greater risk), prior warfarin use, level of renal impairment, geographic region, ELIQUIS dose, type of AF, and aspirin use at randomization (Figure 5).

**Figure 5: Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics – ARISTOTLE Study**



At the end of the ARISTOTLE study, warfarin patients who completed the study were generally maintained on a VKA with no interruption of anticoagulation. ELIQUIS patients who completed the study were generally switched to a VKA with a 2-day period of coadministration of ELIQUIS and VKA, so that some patients may not have been adequately anticoagulated after stopping ELIQUIS until attaining a stable and therapeutic INR. During the 30 days following the end of the study, there were 21 stroke or systemic embolism events in the 6791 patients (0.3%) in the ELIQUIS arm compared to 5 in the 6569 patients (0.1%) in the warfarin arm [*see Dosage and Administration (2.5)*].

### **AVERROES**

In AVERROES, patients with nonvalvular atrial fibrillation thought not to be candidates for warfarin therapy were randomized to treatment with ELIQUIS 5 mg orally twice daily (or 2.5 mg twice daily in selected patients) or aspirin 81 to 324 mg once daily. The primary objective of the study was to determine if ELIQUIS was superior to aspirin for preventing the composite outcome of stroke or systemic embolism. AVERROES was stopped early on the basis of a prespecified interim analysis showing a significant reduction in stroke and systemic embolism for ELIQUIS compared to aspirin that was associated with a modest increase in major bleeding (Table 6) [*see Adverse Reactions (6.1)*].

**Table 6: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in AVERROES**

	<b>ELIQUIS N=2807 n (%/year)</b>	<b>Aspirin N=2791 n (%/year)</b>	<b>Hazard Ratio (95% CI)</b>	<b>P-value</b>
Stroke or systemic embolism	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	<0.0001
Stroke				
Ischemic or undetermined	43 (1.37)	97 (3.11)	0.44 (0.31, 0.63)	-
Hemorrhagic	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)	-
MI	24 (0.76)	28 (0.89)	0.86 (0.50, 1.48)	-
All-cause death	111 (3.51)	140 (4.42)	0.79 (0.62, 1.02)	0.068
Vascular death	84 (2.65)	96 (3.03)	0.87 (0.65, 1.17)	-

## 14.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The clinical evidence for the effectiveness of ELIQUIS is derived from the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical trials in adult patients undergoing elective hip (ADVANCE-3) or knee (ADVANCE-2 and ADVANCE-1) replacement surgery. A total of 11,659 patients were randomized in 3 double-blind, multi-national studies. Included in this total were 1866 patients age 75 or older, 1161 patients with low body weight ( $\leq 60$  kg), 2528 patients with Body Mass Index  $\geq 33$  kg/m<sup>2</sup>, and 625 patients with severe or moderate renal impairment.

In the ADVANCE-3 study, 5407 patients undergoing elective hip replacement surgery were randomized to receive either ELIQUIS 2.5 mg orally twice daily or enoxaparin 40 mg subcutaneously once daily. The first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Treatment duration was 32 to 38 days.

In patients undergoing elective knee replacement surgery, ELIQUIS 2.5 mg orally twice daily was compared to enoxaparin 40 mg subcutaneously once daily (ADVANCE-2, N=3057) or enoxaparin 30 mg subcutaneously every 12 hours (ADVANCE-1, N=3195). In the ADVANCE-2 study, the first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. In the ADVANCE-1 study, both ELIQUIS and enoxaparin were initiated 12 to 24 hours post surgery. Treatment duration in both ADVANCE-2 and ADVANCE-1 was 10 to 14 days.

In all 3 studies, the primary endpoint was a composite of adjudicated asymptomatic and symptomatic DVT, nonfatal PE, and all-cause death at the end of the double-blind intended treatment period. In ADVANCE-3 and ADVANCE-2, the primary endpoint was tested for noninferiority, then superiority, of ELIQUIS to enoxaparin. In ADVANCE-1, the primary endpoint was tested for noninferiority of ELIQUIS to enoxaparin.

The efficacy data are provided in Tables 7 and 8.

**Table 7: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Hip Replacement Surgery\***

Events During 35-Day Treatment Period	ADVANCE-3		Relative Risk (95% CI) P-value
	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	
<b>Number of Patients</b>	<b>N=1949</b>	<b>N=1917</b>	
Total VTE <sup>†</sup> /All-cause death	27 (1.39%) (0.95, 2.02)	74 (3.86%) (3.08, 4.83)	0.36 (0.22, 0.54) p<0.0001
<b>Number of Patients</b>	<b>N=2708</b>	<b>N=2699</b>	
All-cause death	3 (0.11%) (0.02, 0.35)	1 (0.04%) (0.00, 0.24)	
PE	3 (0.11%) (0.02, 0.35)	5 (0.19%) (0.07, 0.45)	
Symptomatic DVT	1 (0.04%) (0.00, 0.24)	5 (0.19%) (0.07, 0.45)	
<b>Number of Patients</b>	<b>N=2196</b>	<b>N=2190</b>	
Proximal DVT <sup>‡</sup>	7 (0.32%) (0.14, 0.68)	20 (0.91) (0.59, 1.42)	
<b>Number of Patients</b>	<b>N=1951</b>	<b>N=1908</b>	
Distal DVT <sup>‡</sup>	20 (1.03%) (0.66, 1.59)	57 (2.99%) (2.31, 3.86)	

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

<sup>†</sup> Total VTE includes symptomatic and asymptomatic DVT and PE.

<sup>‡</sup> Includes symptomatic and asymptomatic DVT.

**Table 8: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Knee Replacement Surgery\***

Events during 12-day treatment period	ADVANCE-1			ADVANCE-2		
	ELIQUIS 2.5 mg po bid	Enoxaparin 30 mg sc q12h	Relative Risk (95% CI) P-value	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
<b>Number of Patients</b>	<b>N=1157</b>	<b>N=1130</b>		<b>N=976</b>	<b>N=997</b>	
Total VTE <sup>†</sup> /All-cause death	104 (8.99%) (7.47, 10.79)	100 (8.85%) (7.33, 10.66)	1.02 (0.78, 1.32) NS	147 (15.06%) (12.95, 17.46)	243 (24.37%) (21.81, 27.14)	0.62 (0.51, 0.74) p<0.0001
<b>Number of Patients</b>	<b>N=1599</b>	<b>N=1596</b>		<b>N=1528</b>	<b>N=1529</b>	
All-cause death	3 (0.19%) (0.04, 0.59)	3 (0.19%) (0.04, 0.59)		2 (0.13%) (0.01, 0.52)	0 (0%) (0.00, 0.31)	
PE	16 (1.0%) (0.61, 1.64)	7 (0.44%) (0.20, 0.93)		4 (0.26%) (0.08, 0.70)	0 (0%) (0.00, 0.31)	
Symptomatic DVT	3 (0.19%) (0.04, 0.59)	7 (0.44%) (0.20, 0.93)		3 (0.20%) (0.04, 0.61)	7 (0.46%) (0.20, 0.97)	
<b>Number of Patients</b>	<b>N=1254</b>	<b>N=1207</b>		<b>N=1192</b>	<b>N=1199</b>	
Proximal DVT <sup>‡</sup>	9 (0.72%) (0.36, 1.39)	11 (0.91%) (0.49, 1.65)		9 (0.76%) (0.38, 1.46)	26 (2.17%) (1.47, 3.18)	
<b>Number of Patients</b>	<b>N=1146</b>	<b>N=1133</b>		<b>N=978</b>	<b>N=1000</b>	
Distal DVT <sup>‡</sup>	83 (7.24%) (5.88, 8.91)	91 (8.03%) (6.58, 9.78)		142 (14.52%) (12.45, 16.88)	239 (23.9%) (21.36, 26.65)	

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

<sup>†</sup> Total VTE includes symptomatic and asymptomatic DVT and PE.

<sup>‡</sup> Includes symptomatic and asymptomatic DVT.

The efficacy profile of ELIQUIS was generally consistent across subgroups of interest for this indication (e.g., age, gender, race, body weight, renal impairment).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

ELIQUIS (apixaban) tablets are available as listed in the table below.

Tablet Strength	Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
2.5 mg	Yellow, round, biconvex	Debossed with “893” on one side and “2½” on the other side	Bottles of 60	0003-0893-21
			Bottles of 180	0003-0893-41
			Hospital Unit-Dose Blister Package of 100	0003-0893-31
5 mg	Pink, oval, biconvex	Debossed with “894” on one side and “5” on the other side	Bottles of 60	0003-0894-21
			Bottles of 180	0003-0894-41
			Hospital Unit-Dose Blister Package of 100	0003-0894-31

### Storage and Handling

Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

*See FDA-approved patient labeling (Medication Guide).*

Advise patients of the following:

- They should not discontinue ELIQUIS without talking to their physician first.
- They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patients have had neuraxial anesthesia or spinal puncture, and particularly if they are taking concomitant medicinal products affecting hemostasis, they should be informed to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel or bladder dysfunction [see *Warnings and Precautions (5.3)*]. If any of these symptoms occur, the patient should contact his or her physician immediately.
- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS [see *Use in Specific Populations (8.1, 8.3)*].

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

Manufactured by:  
Bristol-Myers Squibb Company  
Princeton, New Jersey 08543 USA

Marketed by:  
Bristol-Myers Squibb Company  
Princeton, New Jersey 08543 USA  
and  
Pfizer Inc  
New York, New York 10017 USA

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**MEDICATION GUIDE**  
**ELIQUIS<sup>®</sup>** (ELL eh kwiss)  
**(apixaban)**  
**tablets**

**What is the most important information I should know about ELIQUIS?**

- **For people taking ELIQUIS for atrial fibrillation:**

People with atrial fibrillation (a type of irregular heartbeat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. ELIQUIS lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking ELIQUIS, you may have increased risk of forming a clot in your blood.

**Do not stop taking ELIQUIS without talking to the doctor who prescribes it for you. Stopping ELIQUIS increases your risk of having a stroke.**

ELIQUIS may need to be stopped, if possible, prior to surgery or a medical or dental procedure. Ask the doctor who prescribed ELIQUIS for you when you should stop taking it. Your doctor will tell you when you may start taking ELIQUIS again after your surgery or procedure. If you have to stop taking ELIQUIS, your doctor may prescribe another medicine to help prevent a blood clot from forming.

- **ELIQUIS can cause bleeding** which can be serious and rarely may lead to death. This is because ELIQUIS is a blood thinner medicine that reduces blood clotting.

You may have a higher risk of bleeding if you take ELIQUIS and take other medicines that increase your risk of bleeding, including:

- aspirin or aspirin-containing products
- long-term (chronic) use of nonsteroidal anti-inflammatory drugs (NSAIDs)
- warfarin sodium (COUMADIN<sup>®</sup>, JANTOVEN<sup>®</sup>)
- any medicine that contains heparin
- selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
- other medicines to help prevent or treat blood clots

Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

While taking ELIQUIS:

- you may bruise more easily
- it may take longer than usual for any bleeding to stop

**Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding when taking ELIQUIS:**

- unexpected bleeding, or bleeding that lasts a long time, such as:
  - unusual bleeding from the gums
  - nosebleeds that happen often
  - menstrual bleeding or vaginal bleeding that is heavier than normal
- bleeding that is severe or you cannot control
- red, pink, or brown urine
- red or black stools (looks like tar)
- cough up blood or blood clots
- vomit blood or your vomit looks like coffee grounds
- unexpected pain, swelling, or joint pain
- headaches, feeling dizzy or weak
- **ELIQUIS is not for patients with artificial heart valves.**
- **Spinal or epidural blood clots or bleeding (hematoma).** People who take a blood thinner medicine (anticoagulant) like ELIQUIS, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine

If you take ELIQUIS and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood

clots or bleeding. Tell your doctor right away if you have tingling, numbness, or muscle weakness, especially in your legs and feet.

### **What is ELIQUIS?**

ELIQUIS is a prescription medicine used to:

- reduce the risk of stroke and blood clots in people who have atrial fibrillation.
- reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.

It is not known if ELIQUIS is safe and effective in children.

### **Who should not take ELIQUIS?**

**Do not take ELIQUIS if you:**

- currently have certain types of abnormal bleeding.
- have had a serious allergic reaction to ELIQUIS. Ask your doctor if you are not sure.

### **What should I tell my doctor before taking ELIQUIS?**

**Before you take ELIQUIS, tell your doctor if you:**

- have kidney or liver problems
- have any other medical condition
- have ever had bleeding problems
- are pregnant or plan to become pregnant. It is not known if ELIQUIS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ELIQUIS passes into your breast milk. You and your doctor should decide if you will take ELIQUIS or breastfeed. You should not do both.

Tell all of your doctors and dentists that you are taking ELIQUIS. They should talk to the doctor who prescribed ELIQUIS for you, before you have **any** surgery, medical or dental procedure.

**Tell your doctor about all the medicines you take, including** prescription and over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way ELIQUIS works. Certain medicines may increase your risk of bleeding or stroke when taken with ELIQUIS. See **“What is the most important information I should know about ELIQUIS?”**

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

### How should I take ELIQUIS?

- **Take ELIQUIS exactly as prescribed by your doctor.**
- Take ELIQUIS twice every day with or without food.
- Do not change your dose or stop taking ELIQUIS unless your doctor tells you to.
- If you miss a dose of ELIQUIS, take it as soon as you remember. Do not take more than one dose of ELIQUIS at the same time to make up for a missed dose.
- Your doctor will decide how long you should take ELIQUIS. **Do not stop taking it without first talking with your doctor. If you are taking ELIQUIS for atrial fibrillation, stopping ELIQUIS may increase your risk of having a stroke.**
- **Do not run out of ELIQUIS. Refill your prescription before you run out.** When leaving the hospital following hip or knee replacement, be sure that you will have ELIQUIS available to avoid missing any doses.
- If you take too much ELIQUIS, call your doctor or go to the nearest hospital emergency room right away.
- Call your doctor or healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your doctor or healthcare provider may need to check you.

### What are the possible side effects of ELIQUIS?

- See “**What is the most important information I should know about ELIQUIS?**”
- ELIQUIS can cause a skin rash or severe allergic reaction. Call your doctor or get medical help right away if you have any of the following symptoms:
  - chest pain or tightness
  - swelling of your face or tongue
  - trouble breathing or wheezing
  - feeling dizzy or faint

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of ELIQUIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **How should I store ELIQUIS?**

Store ELIQUIS at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep ELIQUIS and all medicines out of the reach of children.**

### **General Information about ELIQUIS**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ELIQUIS for a condition for which it was not prescribed. Do not give ELIQUIS to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ELIQUIS that is written for health professionals.

For more information, call 1-855-354-7847 (1-855-ELIQUIS) or go to [www.ELIQUIS.com](http://www.ELIQUIS.com).

### **What are the ingredients in ELIQUIS?**

Active ingredient: apixaban.

Inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:  
Bristol-Myers Squibb Company  
Princeton, New Jersey 08543 USA

Marketed by:  
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Revised March 2014