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: DISCONTINUING ELIQUIS IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE
See full prescribing information for complete boxed warning.

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. (2.4, 5.1)

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)

DOSAGE AND ADMINISTRATION

- 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)

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. (5.3)

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*

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or 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 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)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS *

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FULL PRESCRIBING INFORMATION

WARNING: DISCONTINUING ELIQUIS IN PATIENTS 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 (2.4) and Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

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

2.2 Dosage Adjustments

The recommended dose of ELIQUIS is 2.5 mg twice daily in patients with any 2 of the following characteristics:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

CYP3A4 and P-gp inhibitors: 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 Discontinuation 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.

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 INR measurements during coadministration with 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)]*. No data inform use in patients with creatinine clearance <15 mL/min or on dialysis.

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 (i.e., anaphylactic reactions) *[see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Stroke with Discontinuation of ELIQUIS

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. If ELIQUIS must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant *[see Dosage and Administration (2.3)]*.

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 inhibitor, 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 about 24 hours after the last dose, i.e., for about two half-lives. A specific antidote for ELIQUIS is not available. Because of high plasma protein binding, apixaban is not expected to be dialyzable *[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 Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS has 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.

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 ≥12 months for 9375 patients and ≥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 patients-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

	ELIQUIS N=9088 n (%/year)	**Warfarin N=9052 n (%/year)**	**Hazard Ratio (95% CI*)**	**P-value**
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Gastrointestinal (GI)‡	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§	32 (0.21)	22 (0.14)	1.42 (0.83, 2.45)	-
Fatal¶	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
CRNM**	318 (2.08)	444 (3.00)	0.70 (0.60, 0.80)	<0.0001

* Confidence interval.

† 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.

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

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

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

** 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, $CHADS_2$ 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 AF, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0%/year) than did subjects without diabetes (1.9%/year).

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

Subgroup	No. of Patients	No. of Events (% per yr) Apixaban	Warfarin	P-value for Interaction
All Patients	18140	327 (2.13)	462 (3.09)	
Prior Warfarin/VKA Status				0.50
Experienced	10376	185 (2.1)	274 (3.2)	
Naïve	7764	142 (2.2)	188 (3.0)	
Age				0.64
<65 yrs old	5455	56 (1.2)	72 (1.5)	
≥65 to <75 yrs old	7030	120 (2.0)	166 (2.8)	
≥75 yrs old	5655	151 (3.3)	224 (5.2)	
Gender				0.08
Male	11747	225 (2.3)	294 (3.0)	
Female	6393	102 (1.9)	168 (3.3)	
Weight				0.22
≤60 kg	1978	36 (2.3)	62 (4.3)	
>60 kg	16102	290 (2.1)	398 (3.0)	
Type of Atrial Fibrillation				0.75
Permanent/Persistent	15361	283 (2.2)	402 (3.2)	
Paroxysmal	2776	44 (1.9)	60 (2.6)	
Prior Stroke or TIA				0.71
Yes	3422	77 (2.8)	106 (3.9)	
No	14718	250 (2.0)	356 (2.9)	
Diabetes Mellitus				0.003
Yes	4526	112 (3.0)	114 (3.1)	
No	13614	215 (1.9)	348 (3.1)	
Heart Failure				0.30
Yes	5527	87 (1.9)	137 (3.1)	
No	12613	240 (2.2)	325 (3.1)	
$CHADS_2$ Score				0.40
≤1	6169	76 (1.4)	126 (2.3)	
=2	6492	125 (2.3)	163 (3.0)	
≥3	5479	126 (2.9)	173 (4.2)	
Level of Renal Impairment				0.03
Severe or Moderate	3005	73 (3.2)	142 (6.4)	
Mild	7565	157 (2.5)	199 (3.2)	
Normal	7496	96 (1.5)	119 (1.8)	
Apixaban Dose				0.21
2.5 mg BID or placebo	826	20 (3.3)	37 (6.7)	
5 mg BID or placebo	17314	307 (2.1)	425 (3.0)	
Geographic Region				0.16
North America	4463	106 (2.8)	137 (3.6)	
Latin America	3460	60 (2.1)	94 (3.5)	
Europe	7313	110 (1.7)	135 (2.2)	
Asia/Pacific	2904	51 (2.1)	96 (4.1)	
Aspirin at Randomization				0.40
Yes	5608	129 (2.7)	164 (3.7)	
No	12532	198 (1.9)	298 (2.8)	

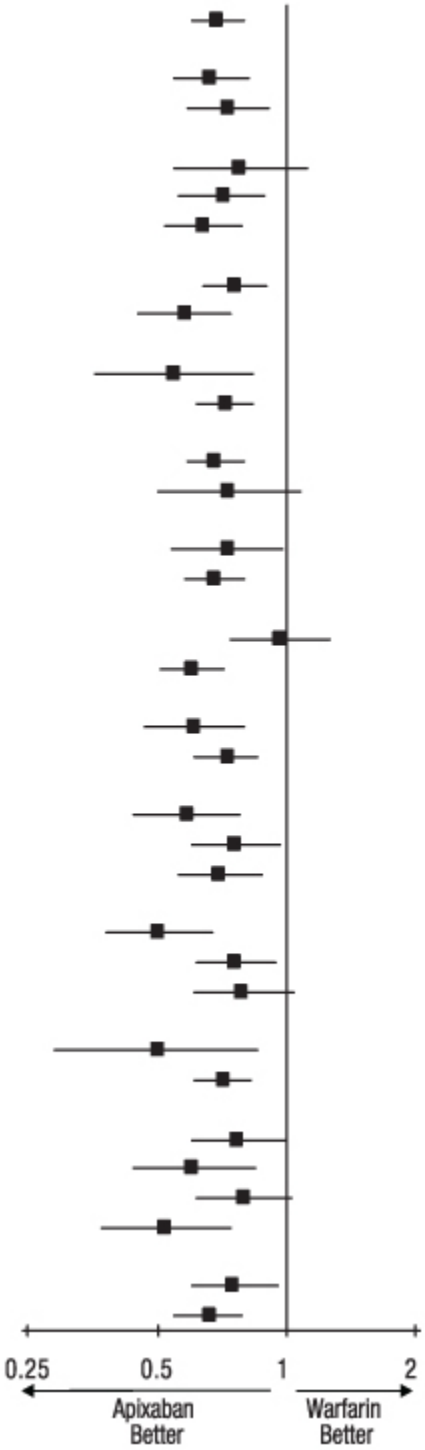


Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2978 n (%/year)	**Aspirin N=2780 n (%/year)**	**Hazard Ratio (95% CI)**	**P-value**
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.

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

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 both 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%/year with apixaban versus 0.62%/year with placebo in patients receiving single antiplatelet therapy and was 5.91%/year with apixaban versus 2.50%/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 ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

8.3 Nursing Mothers

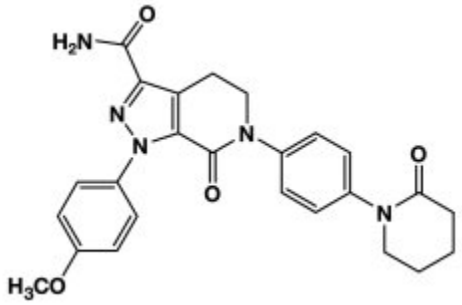
It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).
Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS therapy, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
Of the total subjects in clinical studies of apixaban, >69% were 65 and older, and >31% were 75 and older. The effects of ELIQUIS on the risk of stroke and major bleeding compared to warfarin were maintained in geriatric subjects.

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. Mean apparent 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, indicating that charcoal blocked the continued absorption of apixaban from the gut *[see Clinical Pharmacology (12.3)]*. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion by leading to a more rapid fall in apixaban blood levels.

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-1*H*-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 an oral, reversible, and selective active site 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® 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, enoxaparin, and naproxen were conducted. No pharmacodynamic interactions were observed with aspirin or clopidogrel, but 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 displays prolonged absorption. Thus, despite a short clearance half-life of about 6 hours, the apparent half-life during repeat dosing is about 12 hours, which allows twice-daily dosing to provide effective anticoagulation, but it also means that when the drug is stopped for surgery, anticoagulation persists for at least a day.

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. Apixaban is absorbed throughout the gastrointestinal tract with the distal small bowel and ascending colon contributing about 55% of apixaban absorption. 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.

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

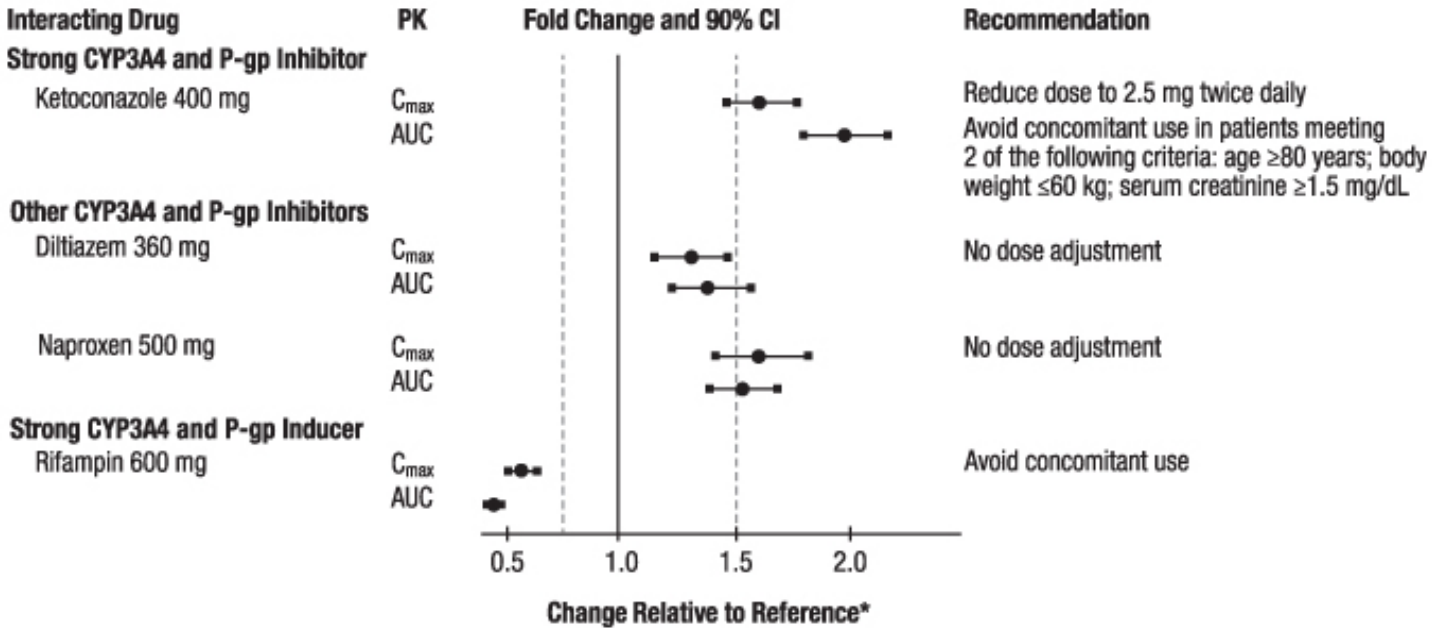
Following intravenous administration, apixaban is eliminated with a dominant half-life of ~5 hours. Following oral administration, the apparent half-life is ~12 hours because of prolonged absorption.

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



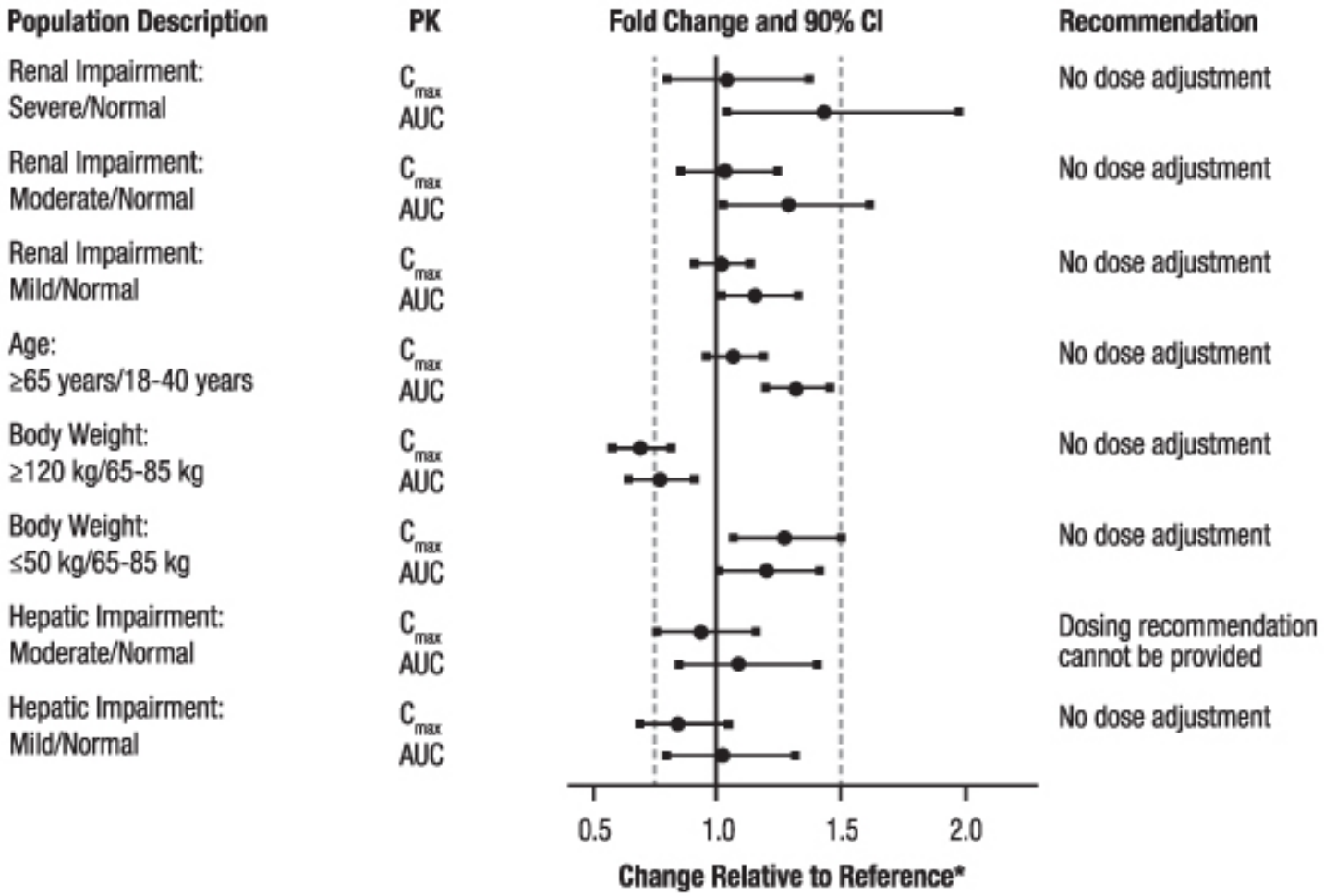
* Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations. Dosing recommendations were also informed by clinical considerations *[see Warnings and Precautions (5.2) and Drug Interactions (7)]*.

In dedicated studies conducted in healthy subjects, famotidine, atenolol, 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, or acetylsalicylic acid.

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

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



* 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.

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_1 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_1-generation female offspring were limited to decreased mating and fertility indices at 1000 mg/kg/day.

14 CLINICAL STUDIES

14.1 ARISTOTLE

Evidence for the efficacy and safety of ELIQUIS was derived from ARISTOTLE, a multinational, double-blind study in patients with nonvalvular atrial fibrillation (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 ≥80 years, body weight ≤60 kg, or serum creatinine ≥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 ≥75 years
- arterial hypertension requiring treatment
- diabetes mellitus
- heart failure ≥New York Heart Association Class 2
- left ventricular ejection fraction ≤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 ≤30 consecutive days of treatment with warfarin or another VKA before entering the study. The mean age was 69 years and the mean $CHADS_2$ 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 ≤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 3 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.

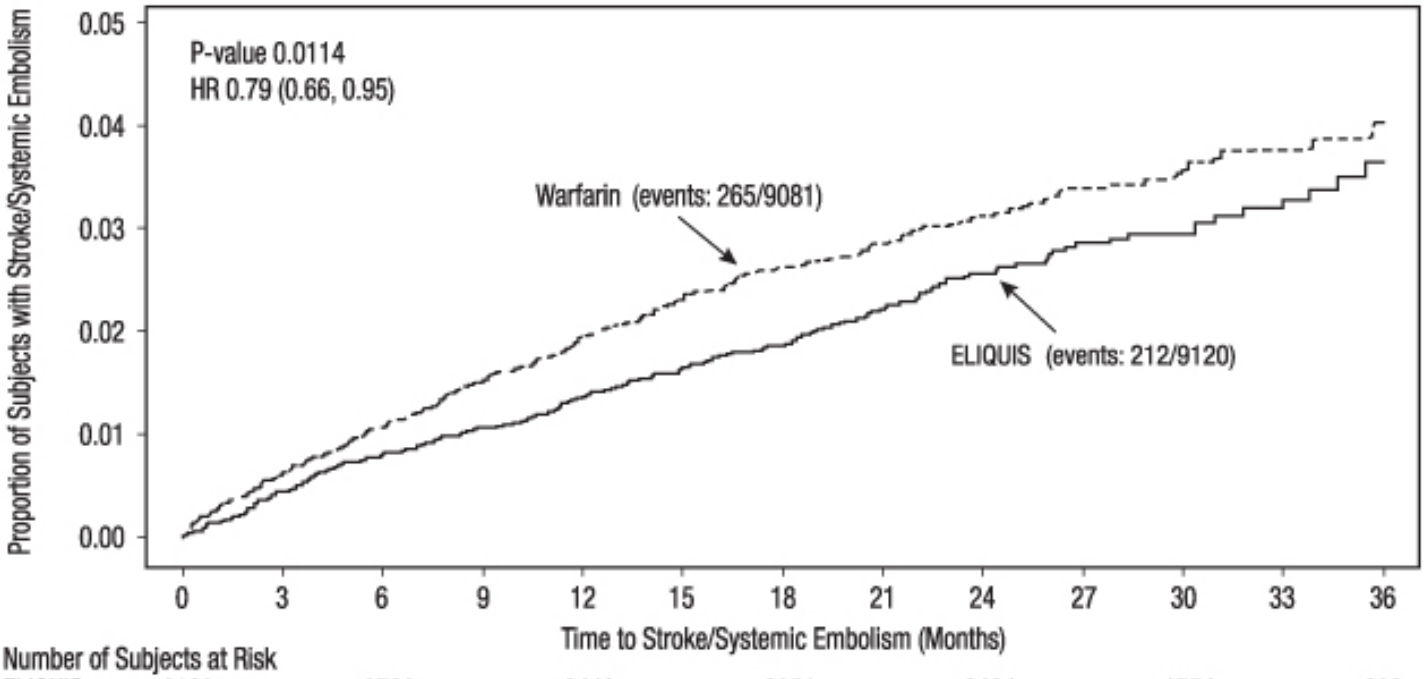
ELIQUIS also showed significantly fewer major bleeds than warfarin *[see Adverse Reactions (6.1)]*.

Table 3: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE (Intent-to-Treat Analysis)

	ELIQUIS N=9120 n (%/year)	**Warfarin N=9081 n (%/year)**	**Hazard Ratio (95% CI)**	**P-value**
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)



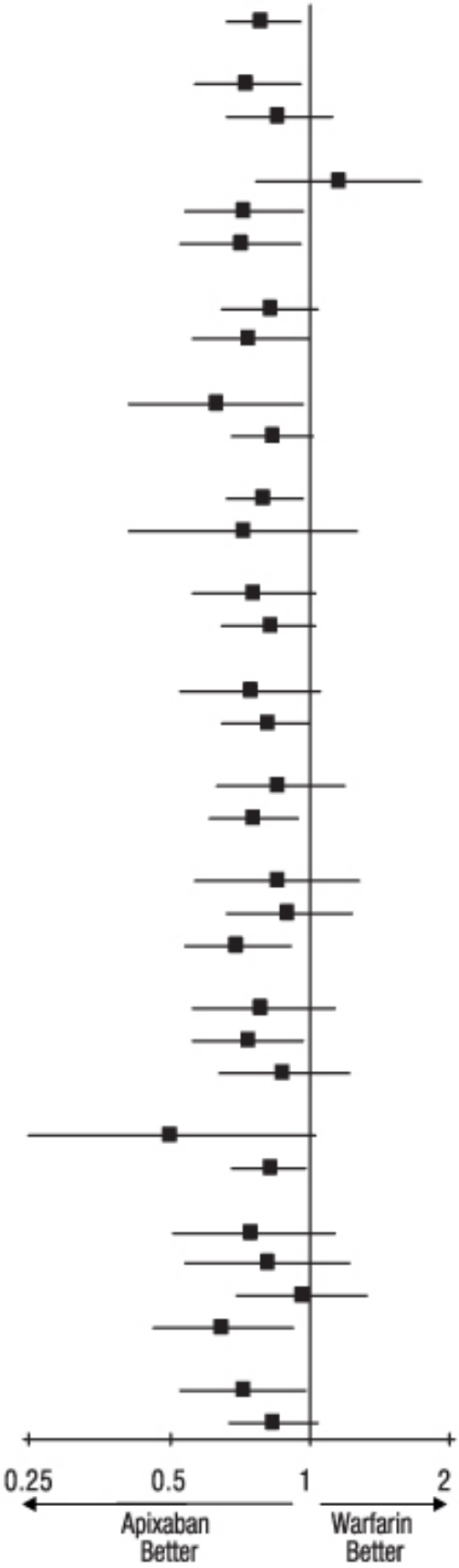
Number of Subjects at Risk							
ELIQUIS	9120	8726	8440	6051	3464	1754	600
Warfarin	9081	8620	8301	5972	3405	1768	572

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, $CHADS_2$ 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

Subgroup	No. of Patients	No. of Events (% per yr) Apixaban	Warfarin	P-value for Interaction
All Patients	18201	212 (1.27)	265 (1.60)	
Prior Warfarin/VKA Status				0.39
Experienced	10401	102 (1.1)	138 (1.5)	
Naïve	7800	110 (1.5)	127 (1.8)	
Age				0.12
<65 yrs old	5471	51 (1.0)	44 (0.9)	
≥65 to <75 yrs old	7052	82 (1.3)	112 (1.7)	
≥75 yrs old	5678	79 (1.6)	109 (2.2)	
Gender				0.60
Male	11785	132 (1.2)	160 (1.5)	
Female	6416	80 (1.4)	105 (1.8)	
Weight				0.26
≤60 kg	1985	34 (2.0)	52 (3.2)	
>60 kg	16154	177 (1.2)	212 (1.4)	
Type of Atrial Fibrillation				0.70
Permanent/Persistent	15412	191 (1.4)	235 (1.7)	
Paroxysmal	2786	21 (0.8)	30 (1.1)	
Prior Stroke or TIA				0.71
Yes	3436	73 (2.5)	98 (3.2)	
No	14765	139 (1.0)	167 (1.2)	
Diabetes Mellitus				0.71
Yes	4547	57 (1.4)	75 (1.9)	
No	13654	155 (1.2)	190 (1.5)	
Heart Failure				0.50
Yes	5541	70 (1.4)	79 (1.6)	
No	12660	142 (1.2)	186 (1.6)	
$CHADS_2$ Score				0.45
≤1	6183	44 (0.7)	51 (0.9)	
=2	6516	74 (1.2)	82 (1.4)	
≥3	5502	94 (1.9)	132 (2.8)	
Level of Renal Impairment				0.72
Severe or Moderate	3017	54 (2.1)	69 (2.7)	
Mild	7587	87 (1.2)	116 (1.7)	
Normal	7518	70 (1.0)	79 (1.1)	
Apixaban Dose				0.22
2.5 mg BID or placebo	831	12 (1.7)	22 (3.3)	
5 mg BID or placebo	17370	200 (1.3)	243 (1.5)	
Geographic Region				0.44
North America	4474	42 (1.0)	56 (1.3)	
Latin America	3468	43 (1.4)	52 (1.8)	
Europe	7343	75 (1.1)	77 (1.1)	
Asia/Pacific	2916	52 (2.0)	80 (3.1)	
Aspirin at Randomization				0.44
Yes	5632	70 (1.3)	94 (1.9)	
No	12569	142 (1.2)	171 (1.5)	



14.2 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 4); *[see Adverse Reactions (6.1)]*.

Table 4: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2807 n (%/year)	**Aspirin 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				
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)	-

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.

- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intends 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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1289808 / 1298500 / 1289807
Issued December 2012

MEDICATION GUIDE

ELIQUIS® (ELL eh kwiss)
(apixaban)
tablets

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

- 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®, JANTOVEN®)
- 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.**

What is ELIQUIS?
ELIQUIS is a prescription medicine used to reduce the risk of stroke and blood clots in people who have atrial fibrillation.
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. Stopping ELIQUIS may increase your risk of having a stroke.**

- **Do not run out of ELIQUIS. Refill your prescription before you run out.**

- 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.

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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and
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New York, New York 10017 USA

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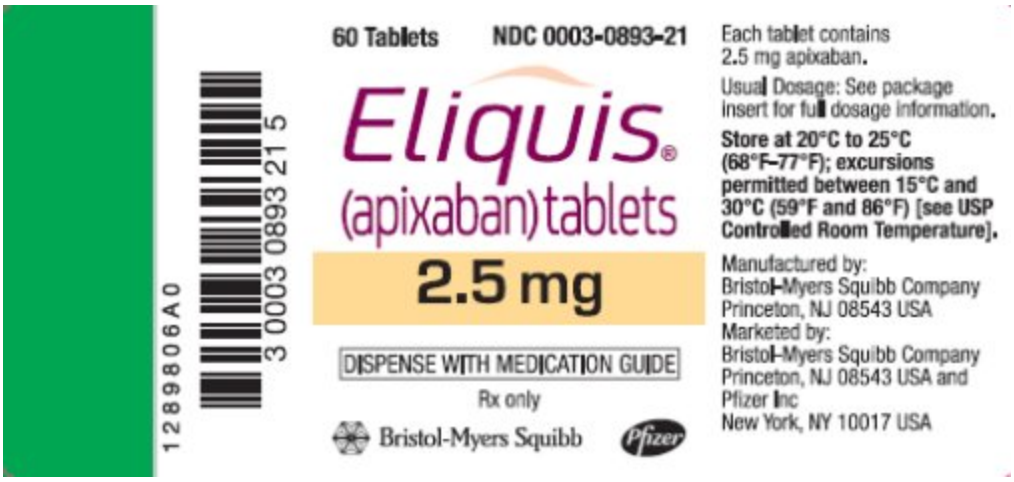
1295958
Issued December 2012

REPRESENTATIVE PACKAGING

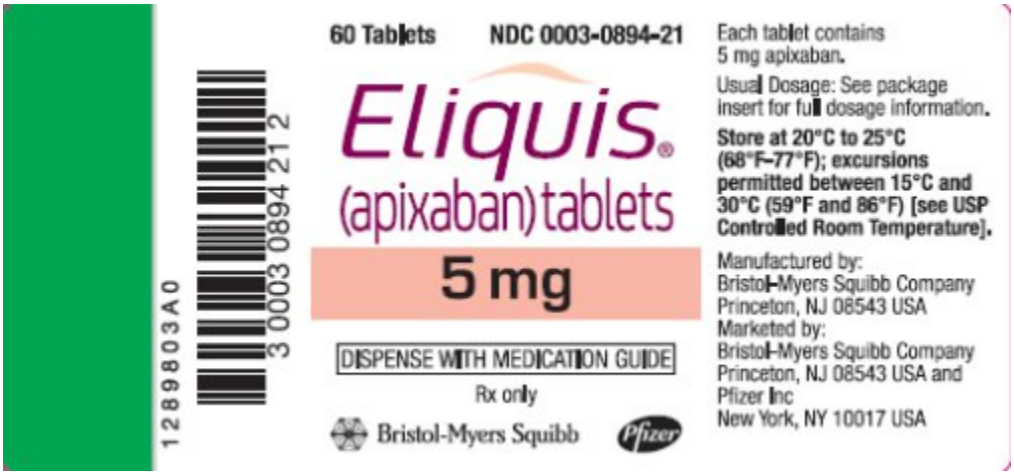
See **How Supplied** section for a complete list of available packages of ELIQUIS.

60 Tablets
NDC 0003-0893-21

ELIQUIS®
(apixaban) tablets
2.5 mg
DISPENSE WITH MEDICATION GUIDE
Rx only
Bristol-Myers Squibb
Pfizer



60 Tablets
NDC 0003-0894-21
ELIQUIS®
(apixaban) tablets
5 mg
DISPENSE WITH MEDICATION GUIDE
Rx only
Bristol-Myers Squibb
Pfizer



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