ELIQUIS® (apixaban) tablets, for oral use

Initial U.S. Approval: 2012

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**INDICATIONS AND USAGE**

ELIQUIS is a factor Xa inhibitor 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)
- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. (1.3, 1.4, 1.5)

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**DOSAGE AND ADMINISTRATION**

- **Reduction of 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 greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. (2.1)

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**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.

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**DRUG INTERACTIONS**

- Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of apixaban. Reduce ELIQUIS dose or avoid coadministration. (2.5, 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)

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**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Not recommended. (8.1)
- Nursing Mothers: Discontinue drug or discontinue nursing. (8.3)
- Severe Hepatic Impairment: Not recommended. (8.7, 12.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 11/2017
1. INDICATIONS AND USAGE

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

ELIQUIS® (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.

1.3 Treatment of Deep Vein Thrombosis

ELIQUIS is indicated for the treatment of DVT.

1.4 Treatment of Pulmonary Embolism

ELIQUIS is indicated for the treatment of PE.

1.5 Reduction in the Risk of Recurrence of DVT and PE

ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

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

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

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.

Treatment of DVT and PE

The recommended dose of ELIQUIS is 10 mg taken orally twice daily for the first 7 days of therapy. After 7 days, the recommended dose is 5 mg taken orally twice daily.

3. DOSAGE FORMS AND STRENGTHS

- 2.5 mg, pink, oval-shaped, biconvex, film-coated tablets with “894” debossed on one side and “2½” on the other side.
- 5 mg, pink, oval-shaped, biconvex, film-coated tablets with “895” 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 Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including 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 atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [see Dosage and Administration (2.4) and Clinical Studies (14.1)].

5.2 Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding [see Dosage and Administration (2.1) 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)].

Advise patients of symptoms and signs of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

Reversal of Anticoagulant Effect

A specific antidote for ELIQUIS is not available, and there is no established way to reverse bleeding in patients taking ELIQUIS. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical studies [see Clinical Pharmacology (12.2)]. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration [see Overdosage (10)].

Hemodilution does not appear to have a substantial impact on apixaban exposure [see Clinical Pharmacology (12.3)]. Protamine sulfate and vitamin K are not 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 no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban, and they are not expected to be effective as a reversal agent.

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.

Monitor patients frequently 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.

5.5 Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of thrombotic events after premature discontinuation [see Warnings and Precautions (5.1)]
- Bleeding [see Warnings and Precautions (5.2)]
- Spinal/epidural anesthesia or puncture [see Warnings and Precautions (5.3)]

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 Patients with 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 ≥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 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 100 patient-years) in ARISTOTLE and AVERROES.

| Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE* |
|---------------------------------------------------------------|-----------------|-------------------|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | ELIQUIS | | Warfarin | | Hazard Ratio | | P-value |
| | N=9088 n (per 100 pt-year) | | N=9052 n (per 100 pt-year) | | ** | | ** |
| Major† | 327 (2.13) | 462 (3.09) | 0.69 (0.60, 0.80) | <0.0001 |
| Intracranial (ICH)‡ | 52 (0.33) | 125 (0.82) | 0.41 (0.30, 0.57) | |
| Hemorrhagic stroke§ | 38 (0.24) | 74 (0.49) | 0.51 (0.34, 0.75) | |
| Other ICH | 15 (0.10) | 51 (0.34) | 0.29 (0.16, 0.51) | |
| Gastrointestinal (GI) ¶ | 128 (0.83) | 141 (0.93) | 0.89 (0.70, 1.14) | |
| Fatal** | 10 (0.06) | 37 (0.24) | 0.27 (0.13, 0.53) | |
| Intracranial | 4 (0.03) | 30 (0.20) | 0.13 (0.05, 0.37) | |
| Non-intracranial | 6 (0.04) | 7 (0.05) | 0.84 (0.28, 2.15) | |

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).
† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intracranial, periocular, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.
‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.
¶ GI bleed includes upper GI, lower GI, and rectal bleeding.
** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, CHA2DS2 score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, 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).
In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

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.
ELIQUIS® (apixaban)

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

<table>
<thead>
<tr>
<th>Bleeding Endpoint*</th>
<th>ADVANCE-3 Hip Replacement Surgery</th>
<th>ADVANCE-2 Knee Replacement Surgery</th>
<th>ADVANCE-1 Knee Replacement Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ELIQUIS 2.5 mg po bid 35±3 days</td>
<td>Enoxaparin 40 mg sc q12h 35±3 days</td>
<td>ELIQUIS 2.5 mg po bid 12±2 days</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 40 mg sc q2d 12±2 days</td>
<td>Enoxaparin 40 mg sc q2d 12±2 days</td>
<td>Enoxaparin 30 mg sc q12h 12±2 days</td>
</tr>
<tr>
<td></td>
<td>First dose 12 to 24 hours post surgery</td>
<td>First dose 9 to 15 hours prior to surgery</td>
<td>First dose 12 to 24 hours post surgery</td>
</tr>
<tr>
<td>Bleed at critical site†</td>
<td>1 (0.04%)</td>
<td>1 (0.04%)</td>
<td>1 (0.07%)</td>
</tr>
<tr>
<td>Major + CRNM†</td>
<td>129 (4.83%)</td>
<td>134 (5.04%)</td>
<td>53 (3.53%)</td>
</tr>
<tr>
<td>All</td>
<td>313 (11.71%)</td>
<td>334 (12.56%)</td>
<td>104 (6.93%)</td>
</tr>
</tbody>
</table>

*All bleeding criteria included surgical site bleeding.
†Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).
§Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).
¶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 ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ELIQUIS, n (%)</th>
<th>Enoxaparin, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>153 (2.6)</td>
<td>159 (2.7)</td>
</tr>
<tr>
<td>Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)</td>
<td>153 (2.6)</td>
<td>178 (3.0)</td>
</tr>
<tr>
<td>Contusion</td>
<td>83 (1.4)</td>
<td>115 (1.9)</td>
</tr>
<tr>
<td>Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)</td>
<td>67 (1.1)</td>
<td>81 (1.4)</td>
</tr>
<tr>
<td>Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture-site hematoma, and catheter-site hemorrhage)</td>
<td>54 (0.9)</td>
<td>60 (1.0)</td>
</tr>
<tr>
<td>Transaminases increased (including alanine aminotransferase and alanine aminotransferase abnormal)</td>
<td>50 (0.8)</td>
<td>71 (1.2)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>47 (0.8)</td>
<td>69 (1.2)</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>38 (0.6)</td>
<td>65 (1.1)</td>
</tr>
</tbody>
</table>

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

Table 5: Bleeding Results in the AMPLIFY Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ELIQUIS N=2676 n (%)</th>
<th>Enoxaparin/Warfarin N=2689 n (%)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>15 (0.6)</td>
<td>49 (1.8)</td>
<td>0.31 (0.17, 0.55)</td>
</tr>
<tr>
<td>CRNM†</td>
<td>103 (3.9)</td>
<td>215 (8.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major + CRNM†</td>
<td>115 (4.3)</td>
<td>261 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>313 (11.7)</td>
<td>505 (18.8)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>402 (15.0)</td>
<td>676 (25.1)</td>
<td></td>
</tr>
</tbody>
</table>

*CRNM = clinically relevant nonmajor bleeding.

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

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ELIQUIS N=2676 n (%)</th>
<th>Enoxaparin/Warfarin N=2689 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>77 (2.9)</td>
<td>146 (5.4)</td>
</tr>
<tr>
<td>Contusion</td>
<td>49 (1.8)</td>
<td>97 (3.6)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>46 (1.7)</td>
<td>102 (3.8)</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>38 (1.4)</td>
<td>30 (1.1)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>35 (1.3)</td>
<td>76 (2.8)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>32 (1.2)</td>
<td>31 (1.2)</td>
</tr>
<tr>
<td>Rectal hemorrhage</td>
<td>26 (1.0)</td>
<td>39 (1.5)</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>26 (1.0)</td>
<td>50 (1.9)</td>
</tr>
</tbody>
</table>

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

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

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematomas, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.
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 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban versus 2.5% 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 concomitant use of aspirin and warfarin increased the bleeding risk 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 based on area under the 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 area under plasma-concentration time curve) 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 the ARISTOTLE and AVERROES clinical studies, >89% 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. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 and older and >13% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

8.6 Renal Impairment

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

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics [see Dosage and Administration (2.1)]:

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usual recommended dose [see Dosage and Administration (2.1)] will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study [see Clinical Pharmacology (12.3)]. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.
Propylthiouracil (PTU), iodine, and salicylates also inhibit hepatic metabolism of apixaban.

8.2.1.4 Effect of Steroid Preparations on Pharmacokinetics
Steroid preparations, including corticosteroids and androgens, were found to deplete apixaban concentrations. As a result, patients receiving corticosteroids and androgens may have an increased risk of bleeding. Patients with known bleeding risk or receiving other warfarin, antiplatelet, or anticoagulant treatments should be monitored closely.

8.2.1.5 Effect of CYP2C9 Modulators
Azythromycin, ketoconazole, and ciprofibrate were found to inhibit CYP2C9 and did not significantly affect apixaban concentrations.

8.2.1.6 Effect of Other Drug Interactions
Apixaban had no effect on warfarin, aspirin, clopidogrel, enoxaparin, and naproxen.

8.2.1.7 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.8 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.9 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.10 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.11 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.12 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.13 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.14 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.15 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.16 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.17 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.18 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.19 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.20 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.21 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.22 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.23 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.24 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.25 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.26 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.27 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.28 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.29 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.30 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.31 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.32 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.33 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.34 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.35 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.36 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.37 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.38 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.39 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.

8.2.1.40 Effect of Concomitant Drugs on ETP
The addition of PCCs to the apixaban regimen increased endogenous thrombin potential by 50% to 60%.
The effects of coadministered drugs on the pharmacokinetics of apixaban 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**

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>PK</th>
<th>Fold Change and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong CYP3A4 and P-gp Inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole 400 mg</td>
<td>C\textsubscript{max} AUC</td>
<td></td>
</tr>
<tr>
<td>Other CYP3A4 and P-gp Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem 360 mg</td>
<td>C\textsubscript{max} AUC</td>
<td></td>
</tr>
<tr>
<td>Naproxen 500 mg</td>
<td>C\textsubscript{max} AUC</td>
<td></td>
</tr>
<tr>
<td><strong>Strong CYP3A4 and P-gp Inducer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin 600 mg</td>
<td>C\textsubscript{max} AUC</td>
<td></td>
</tr>
</tbody>
</table>

Change Relative to Reference

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

**Hemodialysis in ESRD subjects:** Systemic exposure to apixaban administered as a single 5 mg dose in ESRD subjects dosed immediately after the completion of a 4-hour hemodialysis session (post-dialysis) is 36% higher when compared to subjects with normal renal function (Figure 3).

The systemic exposure to apixaban administered 2 hours prior to 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 is 17% higher compared to those with normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min. The systemic exposure of apixaban is 14% lower on dialysis when compared to not on dialysis.

Protein binding was similar (92%-94%) between healthy controls and ESRD subjects during 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\textsubscript{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\textsubscript{1} 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 ≥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\textsubscript{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%,
ELIQUIS® (apixaban)

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 9 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 9: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE (Intent-to-Treat Analysis)

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS</th>
<th>Warfarin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>N=9120</td>
<td>n (%/year)</td>
<td>212 (1.27)</td>
<td>265 (1.60)</td>
</tr>
<tr>
<td>Stroke</td>
<td>n=9081</td>
<td>n (%/year)</td>
<td>199 (1.19)</td>
<td>250 (1.51)</td>
</tr>
<tr>
<td>Ischemic without hemorrhage</td>
<td></td>
<td></td>
<td>140 (0.83)</td>
<td>136 (0.82)</td>
</tr>
<tr>
<td>Ischemic with hemorrhagic conversion</td>
<td></td>
<td></td>
<td>12 (0.07)</td>
<td>20 (0.12)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td></td>
<td>40 (0.24)</td>
<td>78 (0.47)</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td>14 (0.08)</td>
<td>21 (0.13)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td></td>
<td></td>
<td>15 (0.09)</td>
<td>17 (0.10)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n of Events / N of Patients (% per year)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>212 / 9120 (1.3)</td>
<td>265 / 9081 (1.6)</td>
</tr>
<tr>
<td>Prior Warfarin/VKA Status</td>
<td>102 / 5208 (1.1)</td>
<td>138 / 5193 (1.5)</td>
</tr>
<tr>
<td>Age</td>
<td>51 / 2731 (1.0)</td>
<td>44 / 2740 (0.9)</td>
</tr>
<tr>
<td>CHADS 2 Score</td>
<td>57 / 2284 (1.4)</td>
<td>75 / 2263 (1.9)</td>
</tr>
<tr>
<td>Weight</td>
<td>34 / 1018 (2.0)</td>
<td>52 / 967 (3.2)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>57 / 2284 (1.4)</td>
<td>75 / 2263 (1.9)</td>
</tr>
<tr>
<td>Geographic Region</td>
<td>6 / 137 (2.8)</td>
<td>10 / 133 (5.1)</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>18 / 1720 (0.9)</td>
<td>26 / 2246 (1.2)</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>31 / 1720 (0.9)</td>
<td>39 / 1697 (1.2)</td>
</tr>
<tr>
<td>Aspirin at Randomization</td>
<td>70 / 2659 (1.3)</td>
<td>94 / 2773 (1.9)</td>
</tr>
<tr>
<td>CHADS 2 Score</td>
<td>44 / 3100 (0.7)</td>
<td>51 / 3083 (0.9)</td>
</tr>
<tr>
<td>CHADS 2 Score</td>
<td>74 / 3262 (1.2)</td>
<td>82 / 3254 (1.4)</td>
</tr>
<tr>
<td>CHADS 2 Score</td>
<td>94 / 2758 (2.0)</td>
<td>132 / 2744 (2.6)</td>
</tr>
</tbody>
</table>
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 (2.4)].

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 10) [see Adverse Reactions (6.1)].

Table 10: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in AVERROES

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ELIQUIS 2.5 mg po bid</th>
<th>Aspirin 325 mg po qid</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/systemic embolism</td>
<td>51/1490 (3.42)</td>
<td>113/1490 (3.63)</td>
<td>0.45 (0.32, 0.62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>43/1490 (2.87)</td>
<td>97/1490 (3.11)</td>
<td>0.44 (0.31, 0.63)</td>
<td></td>
</tr>
<tr>
<td>Ischemic or undetermined</td>
<td>6/1490 (0.41)</td>
<td>9/1490 (0.59)</td>
<td>0.67 (0.24, 1.88)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>3/1490 (0.20)</td>
<td>13/1490 (0.87)</td>
<td>0.15 (0.03, 0.68)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>24/1490 (1.60)</td>
<td>28/1490 (1.87)</td>
<td>0.86 (0.50, 1.48)</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>111/1345 (8.28)</td>
<td>140/1345 (10.42)</td>
<td>0.79 (0.62, 1.02)</td>
<td>0.068</td>
</tr>
<tr>
<td>Vascular death</td>
<td>64/1345 (4.75)</td>
<td>96/1345 (7.19)</td>
<td>0.87 (0.65, 1.17)</td>
<td></td>
</tr>
</tbody>
</table>

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 (<60 kg), 2528 patients with Body Mass Index ≥33 kg/m², 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 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 11 and 12.

Table 11: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Hip Replacement Surgery

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

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

Table 12: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Knee Replacement Surgery

<table>
<thead>
<tr>
<th>Events during 12-day treatment period</th>
<th>ELIQUIS 2.5 mg po bid</th>
<th>Enoxaparin 30 mg sc q12h</th>
<th>Relative Risk (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>N=1157</td>
<td>N=1130</td>
<td></td>
</tr>
<tr>
<td>Total VTE/All-cause death</td>
<td>104 (8.99%) (747, 1709)</td>
<td>100 (8.58%) (733, 1066)</td>
<td>1.02 (0.78, 1.32) NS</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>N=1159</td>
<td>N=1196</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>3 (0.19%) (0.04, 0.59)</td>
<td>3 (0.19%) (0.04, 0.59)</td>
<td>2.0 (0.13%) (0.01, 0.52) 0 (0%) (0.00, 0.31)</td>
</tr>
<tr>
<td>PE</td>
<td>16 (1.0%) (0.61, 1.64)</td>
<td>7 (0.44%) (0.20, 0.93)</td>
<td>4.0 (0.26%) (0.08, 0.70) 0 (0%) (0.00, 0.31)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>3 (0.19%) (0.04, 0.59)</td>
<td>7 (0.44%) (0.20, 0.93)</td>
<td>3.0 (0.20%) (0.04, 0.61) 7 (0.46%) (0.20, 0.97)</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>N=1254</td>
<td>N=1207</td>
<td></td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>9 (0.72%) (0.36, 1.39)</td>
<td>11 (0.91%) (0.49, 1.65)</td>
<td>9 (0.76%) (0.38, 1.46) 26 (2.17%) (1.47, 3.18)</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>N=1146</td>
<td>N=1133</td>
<td></td>
</tr>
<tr>
<td>Distal DVT</td>
<td>83 (7.24%) (5.88, 9.81)</td>
<td>91 (8.03%) (6.58, 9.78)</td>
<td>142 (14.52%) (12.45, 16.88) 239 (23.9%) (21.36, 26.65)</td>
</tr>
</tbody>
</table>

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

Table:<ref>Table 12: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Knee Replacement Surgery</ref>
14.3 Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

Efficacy and safety of ELIQUIS for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following 6 to 12 months of anticoagulant treatment was derived from the AMPLIFY and AMPLIFY-EXT studies. Both studies were randomized, parallel-group, double-blind trials in patients with symptomatic proximal DVT and/or symptomatic PE. All key safety and efficacy endpoints were adjudicated in a blinded manner by an independent committee.

AMPLIFY

The primary objective of AMPLIFY was to determine whether ELIQUIS was noninferior to enoxaparin/warfarin for the incidence of recurrent VTE (venous thromboembolism) or VTE-related death. Patients with an objectively confirmed symptomatic DVT and/or PE were randomized to treatment with ELIQUIS 10 mg twice daily orally for 7 days followed by ELIQUIS 5 mg twice daily orally for 6 months, or enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR ≥2) followed by warfarin (target INR range 2.0-3.0) orally for 6 months. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent, and patients with creatinine clearance <25 mL/min, significant liver disease, an existing heart valve or atrial fibrillation, or active bleeding were excluded from the AMPLIFY study. Patients were allowed to enter the study with or without prior parenteral anticoagulation (up to 48 hours).

A total of 5244 patients were evaluable for efficacy and were followed for a mean of 154 days in the ELIQUIS group and 152 days in the enoxaparin/warfarin group. The mean age was 57 years. The AMPLIFY study population was 59% male, 83% Caucasian, 8% Asian, and 4% Black. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2.0-3.0) was 60.9%.

Approximately 90% of patients enrolled in AMPLIFY had an unprovoked DVT or PE at baseline. The remaining 10% of patients with a provoked DVT or PE were required to have an additional ongoing risk factor in order to be randomized, which included previous episode of DVT or PE, immobilization, history of cancer, active cancer, and known prothrombotic genotype.

ELIQUIS was shown to be noninferior to enoxaparin/warfarin in the AMPLIFY study for the primary endpoint of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death over 6 months of therapy (Table 13).

### Efficacy Results in the AMPLIFY Study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ELIQUIS (n=2609)</th>
<th>Enoxaparin/Warfarin (n=2635)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE or VTE-related death*</td>
<td>59 (2.3%)</td>
<td>71 (2.7%)</td>
<td>0.84 (0.60, 1.18)</td>
</tr>
<tr>
<td>DVT†</td>
<td>22 (0.8%)</td>
<td>35 (1.3%)</td>
<td>0.63 (0.39, 1.01)</td>
</tr>
<tr>
<td>PE‡</td>
<td>27 (1.0%)</td>
<td>25 (0.9%)</td>
<td>1.08 (0.66, 1.75)</td>
</tr>
<tr>
<td>VTE-related death³</td>
<td>12 (0.4%)</td>
<td>16 (0.6%)</td>
<td>0.76 (0.45, 1.29)</td>
</tr>
<tr>
<td>VTE or all-cause death</td>
<td>84 (3.2%)</td>
<td>104 (4.0%)</td>
<td>0.82 (0.61, 1.08)</td>
</tr>
<tr>
<td>VTE or CV-related death</td>
<td>61 (2.3%)</td>
<td>72 (2.7%)</td>
<td>0.80 (0.57, 1.11)</td>
</tr>
</tbody>
</table>

* Noninferior compared to enoxaparin/warfarin (P-value <0.0001).
† Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

In the AMPLIFY study, patients were stratified according to their index event of PE (with or without DVT) or DVT (without PE). Efficacy in the initial treatment of VTE was consistent between the two subgroups.

AMPLIFY-EXT

Patients who had been treated for DVT and/or PE for 6 to 12 months with anticoagulant therapy without having a recurrent event were randomized to treatment with ELIQUIS 2.5 mg orally twice daily, ELIQUIS 5 mg orally twice daily, or placebo for 12 months. Approximately one-third of patients participated in the AMPLIFY study prior to enrollment in the AMPLIFY-EXT study.

A total of 2482 patients were randomized to study treatment and were followed for a mean of approximately 330 days in the ELIQUIS group and 312 days in the placebo group. The mean age in the AMPLIFY-EXT study was 57 years. The study population was 57% male, 85% Caucasian, 5% Asian, and 3% Black.

The AMPLIFY-EXT study enrolled patients with either an unprovoked DVT or PE at baseline (approximately 92%) or patients with a provoked baseline event and one additional risk factor for recurrence (approximately 8%). However, patients who had experienced multiple episodes of unprovoked DVT or PE were excluded from the AMPLIFY-EXT study. In the AMPLIFY-EXT study, both doses of ELIQUIS were superior to placebo in the primary endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE), or all-cause death (Table 14).

### Efficacy Results in the AMPLIFY-EXT Study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ELIQUIS 2.5 mg bid vs Placebo</th>
<th>ELIQUIS 5 mg bid vs Placebo</th>
<th>ELIQUIS 2.5 mg bid vs Placebo</th>
<th>ELIQUIS 5 mg bid vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE or all-cause death</td>
<td>32 (3.8%)</td>
<td>34 (4.2%)</td>
<td>96 (11.6%)</td>
<td>0.36 (0.22, 0.53)</td>
</tr>
<tr>
<td>DVT*</td>
<td>19 (2.3%)</td>
<td>26 (3.1%)</td>
<td>72 (8.7%)</td>
<td>0.30 (0.17, 0.53)</td>
</tr>
<tr>
<td>PE*</td>
<td>23 (2.7%)</td>
<td>25 (3.1%)</td>
<td>37 (4.5%)</td>
<td>0.27 (0.14, 0.51)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>22 (2.6%)</td>
<td>25 (3.1%)</td>
<td>33 (4.0%)</td>
<td>0.82 (0.60, 1.11)</td>
</tr>
</tbody>
</table>

* Patients with more than one event are counted in multiple rows.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Tablet Color/Shape</th>
<th>Tablet Markings</th>
<th>Package Size</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
<td>Yellow, round, biconvex</td>
<td>Debossed with “893” on one side and “125” on the other side</td>
<td>Bottles of 60</td>
<td>0003-0893-21</td>
</tr>
<tr>
<td>5 mg</td>
<td>Pink, oval, biconvex</td>
<td>Debossed with “894” on one side and “5” on the other side</td>
<td>Bottles of 60</td>
<td>0003-0894-21</td>
</tr>
</tbody>
</table>

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

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- 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.
- To 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 patient is having neuraxial anesthesia or spinal puncture, inform the patient to avoid any unusual bleeding to their physician.
- To tell their physicians if they are pregnant or plan to become pregnant or are breast-feeding or intend to breastfeed during treatment with ELIQUIS [see Use in Specific Populations (8.1, 8.3)]. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breast-feeding or intend to breastfeed during treatment with ELIQUIS [see Use in Specific Populations (8.1, 8.3)]. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube [see Dosage and Administration (2.2)].
- What to do if a dose is missed [see Dosage and Administration (2.2)].
What is the most important information I should know about ELIQUIS?

- **For people taking ELIQUIS for atrial fibrilation:**
  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.**

**Spinal or epidural blood clots (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.
• treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism), and reduce the risk of them occurring again.

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.
• If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take ELIQUIS.
• 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.

**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.

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New York, New York 10017 USA

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