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### ELIQUIS® (apixaban)  
**DOSING SUMMARY**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For all indications:</strong> Please see pages 22-23 for additional dosage adjustment information on coadministration with combined P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) inhibitors.</td>
<td>5 mg twice daily in most patients</td>
</tr>
</tbody>
</table>

**Dose adjustment for NVAF patients:**  
2.5 mg twice daily is recommended in patients with at least 2 of the following characteristics:  
- age ≥80 years  
- body weight ≤60 kg  
- serum creatinine ≥1.5 mg/dL  

**Reduction in the risk of stroke/systemic embolism in nonvalvular atrial fibrillation (NVAF)**
<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE)</td>
<td>10 mg twice daily for the first 7 days</td>
</tr>
<tr>
<td></td>
<td>▼ After 7 days, ▼ transition to</td>
</tr>
<tr>
<td></td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>Reduction in the risk of recurrent DVT/PE following initial therapy</td>
<td>2.5 mg twice daily after at least 6 months of treatment for DVT or PE</td>
</tr>
<tr>
<td>Prophylaxis of DVT, which may lead to PE, following hip or knee replacement surgery</td>
<td>2.5 mg twice daily for <strong>35 days</strong> starting 12 to 24 hours after <strong>hip replacement</strong> surgery</td>
</tr>
<tr>
<td></td>
<td>2.5 mg twice daily for <strong>12 days</strong> starting 12 to 24 hours after <strong>knee replacement</strong> surgery</td>
</tr>
</tbody>
</table>
SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS® (apixaban) INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants

Please see additional Important Safety Information on pages 28-36.
Please see attached Full U.S. Prescribing Information, including Boxed WARNINGS, and Medication Guide.
SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (Continued)

- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of ELIQUIS® (apixaban) and neuraxial procedures is not known

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

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.
For patients with NVAF, DOSING FOR REDUCING THE RISK OF STROKE & SYSTEMIC EMBOLISM

5 mg taken orally twice daily recommended for most NVAF patients

Recommended dose
In 2 Phase III NVAF clinical trials, approximately 95% of ELIQUIS® (apixaban) patients received this dose.

Dosage adjustment
For patients with at least 2 of the following:

- age $\geq$ 80 years
- body weight $\leq$ 60 kg
- serum creatinine $\geq$ 1.5 mg/dL

PLEASE SEE PAGES 12-25 FOR ADDITIONAL IMPORTANT DOSING INFORMATION.

Please see attached Full U.S. Prescribing Information, including Boxed WARNINGS, and Medication Guide.
For patients with DVT/PE, DOISING FOR TREATING DVT/PE

10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily, recommended for the treatment of DVT and PE

**Recommended dose**

10 mg (two 5 mg tablets) twice daily

Day 1 to Day 7

5 mg twice daily

Following Day 7

An example of an ELIQUIS® (apixaban) prescription for a patient starting therapy for the treatment of DVT/PE

FOR ADDRESS __________________________

R

ELIQUIS 5 mg tablets
Take 2 tablets by mouth twice daily for 7 days
Followed by 1 tablet by mouth twice daily

First 30 days = 74 tablets
Subsequent prescriptions for a 30-day supply = 60 tablets (take one 5 mg tablet by mouth twice daily)

PLEASE SEE PAGES 12-25 FOR ADDITIONAL IMPORTANT DOSING INFORMATION.
For patients who have experienced a DVT/PE, REDUCING THE RISK OF RECURRENT DVT/PE FOLLOWING INITIAL THERAPY

2.5 mg taken orally twice daily recommended for the reduction in the risk of recurrent DVT/PE following initial therapy

**Recommended dose**

2.5 mg twice daily

**Following ≥6 months of treatment for DVT or PE**

Reduce dose by 50%: For patients receiving ELIQUIS® (apixaban) doses of 5 mg or 10 mg twice daily, when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir).

*Clarithromycin*

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

(Content continues on next page)
In patients already taking ELIQUIS® (apixaban) at a dose of 2.5 mg twice daily: Avoid coadministration with combined P-gp and strong CYP3A4 inhibitors.
For patients who have undergone hip or knee replacement surgery, DOSING FOR PROPHYLAXIS OF DVT, WHICH MAY LEAD TO PE

2.5 mg taken orally twice daily recommended for hip or knee replacement surgery patients

**Recommended dose**

2.5 mg twice daily

The initial dose should be taken 12 to 24 hours after hip or knee replacement surgery

**Recommended treatment duration for patients undergoing**

- **Hip replacement surgery**: 35 days
- **Knee replacement surgery**: 12 days

(Content continues on next page)
In patients already taking ELIQUIS® (apixaban) at a dose of 2.5 mg twice daily: Avoid coadministration with combined P-gp and strong CYP3A4 inhibitors. **Clarithromycin**

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

PLEASE SEE PAGES 12-25 FOR ADDITIONAL IMPORTANT DOSING INFORMATION.
DOSING IN PATIENTS WITH RENAL IMPAIRMENT
ELIQUIS® (apixaban) elimination

Renal excretion accounts for about 27% of total clearance

- ELIQUIS is eliminated in both urine and feces. Biliary and direct intestinal excretion contributes to elimination of ELIQUIS in the feces.
### Dosing Considerations in NVAF Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>No Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>✔️</td>
</tr>
<tr>
<td>Moderate</td>
<td>✔️</td>
</tr>
<tr>
<td>Severe</td>
<td>✔️</td>
</tr>
</tbody>
</table>

**No dose adjustment for renal impairment alone in patients with NVAF** (see pages 2 and 14 for additional dosage adjustment criteria)

**Patients with end-stage renal disease (ESRD) on dialysis:**

- Clinical efficacy and safety studies with ELIQUIS® (apixaban) did not enroll patients with ESRD on dialysis.
- In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study.
- It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as were seen in ARISTOTLE.

Please see attached Full U.S. Prescribing Information, including **Boxed WARNINGS**, and Medication Guide.
Dosing considerations in NVAF patients with renal impairment

5 mg taken orally twice daily recommended for most NVAF patients

**Recommended dose**
In 2 Phase III NVAF clinical trials, approximately 95% of ELIQUIS® (apixaban) patients received this dose.

**Dosage adjustment**
For patients with at least 2 of the following:

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

Please see attached Full U.S. Prescribing Information, including Boxed WARNINGS, and Medication Guide.
Dosing considerations in patients with renal impairment for all other ELIQUIS® (apixaban) indications

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis, for the following indications:

- **Prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery**
- **Treatment of DVT**
- **Treatment of PE**
- **Reduction in the risk of recurrent DVT and PE following initial therapy**

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis.

Please see attached Full U.S. Prescribing Information, including Boxed WARNINGS, and Medication Guide.
**DOSING IN PATIENTS WITH HEPATIC IMPAIRMENT**

**Mild**
hepatic impairment (Child-Pugh class A)

No dose adjustment required

**Moderate**
hepatic impairment (Child-Pugh class B)

There is limited clinical experience with ELIQUIS® (apixaban) in patients with moderate hepatic impairment; dosing recommendation cannot be provided

**Severe**
hepatic impairment (Child-Pugh class C)

ELIQUIS is not recommended

Adjust ELIQUIS dose for patients taking drugs that are combined P-gp and strong CYP3A4 inhibitors.

See Drug Interactions on pages 22-23 for more information.
DOSING CONSIDERATIONS AND ADMINISTRATION OPTIONS

Additional dosing considerations

- Does not require routine monitoring using international normalized ratio (INR) or other tests of coagulation
- No known dietary restrictions
- Can be taken with or without food
- **Missed dose:** If a dose of ELIQUIS® (apixaban) 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
DOSING CONSIDERATIONS AND ADMINISTRATION OPTIONS

Temporary interruption for surgery and other interventions¹

<table>
<thead>
<tr>
<th>Bleeding risk with elective surgery or invasive procedures</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate</strong> or <strong>high risk</strong> of unacceptable or clinically significant bleeding</td>
<td>Discontinue ELIQUIS® (apixaban) at least <strong>48 hours</strong> prior</td>
</tr>
<tr>
<td><strong>Low risk</strong> or <strong>noncritical site</strong> and <strong>easily controlled</strong></td>
<td>Discontinue ELIQUIS at least <strong>24 hours</strong> prior</td>
</tr>
</tbody>
</table>

- Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

Please see attached Full U.S. Prescribing Information, including Boxed WARNINGS, and Medication Guide.
DOSING CONSIDERATIONS AND ADMINISTRATION OPTIONS

Guidance for switching patients to and from ELIQUIS® (apixaban)

Switching from anticoagulants other than warfarin (oral or parenteral) to ELIQUIS:

• Discontinue the anticoagulant other than warfarin and begin taking ELIQUIS at the usual time of the next dose of the anticoagulant other than warfarin

Switching from ELIQUIS to anticoagulants other than warfarin (oral or parenteral):

• Discontinue ELIQUIS and begin taking the new anticoagulant other than warfarin at the usual time of the next dose of ELIQUIS
Switching from ELIQUIS to warfarin:

- ELIQUIS affects INR, so that initial INR measurements during transition to warfarin may not be useful for determining the appropriate dose of warfarin.
- One approach is to discontinue ELIQUIS and begin both parenteral anticoagulant and warfarin at the time the next dose would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

Switching from warfarin to ELIQUIS:

- Discontinue warfarin and start ELIQUIS when the INR is < 2.0.
Administration Options

• For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS® (apixaban) tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally.

• Alternatively, ELIQUIS tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube.

• Crushed ELIQUIS tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.
## DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Combined P-gp and strong CYP3A4 inhibitors</th>
<th>Reduce dose by 50%: For patients receiving ELIQUIS® (apixaban) doses of 5 mg or 10 mg twice daily when coadministered with combined P-gp and strong CYP3A4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>In patients already taking ELIQUIS at a dose of 2.5 mg twice daily:</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>• Avoid coadministration with combined P-gp and strong CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>These drugs increase exposure to ELIQUIS and increase the risk of bleeding</td>
</tr>
</tbody>
</table>

*Clarithromycin*  
*PK data suggest that no dose adjustment is necessary*

---

PK=pharmacokinetic.

(Content continues on next page)
## DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Combined P-gp and strong CYP3A4 inducers</th>
<th>Avoid concomitant use. These drugs decrease exposure to ELIQUIS® (apixaban) and increase the risk of stroke and other thromboembolic events.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>St. John’s wort</td>
<td></td>
</tr>
</tbody>
</table>

These drug categories are examples described in the Full Prescribing Information, not an all-inclusive list.
DRUG INTERACTIONS

Drugs affecting hemostasis
Coadministration with these drugs increases the risk of bleeding:

- Aspirin and other antiplatelet agents
- Other anticoagulants
- Heparin
- Thrombolytic agents
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin norepinephrine reuptake inhibitors (SNRIs)
- Nonsteroidal anti-inflammatory drugs (NSAIDs), when used chronically
- Fibrinolytics

These drug categories are examples described in the Full Prescribing Information, not an all-inclusive list.
**DRUG INTERACTIONS**

**Additional considerations**

- Apixaban is a substrate of both CYP3A4 and P-gp
- Famotidine, atenolol, prasugrel, and enoxaparin did not meaningfully alter the pharmacokinetics of ELIQUIS® (apixaban) in healthy subjects
- ELIQUIS did not meaningfully alter the pharmacokinetics of digoxin, naproxen, atenolol, prasugrel, or acetylsalicylic acid in healthy subjects
- 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
- For diltiazem, no dose adjustment of ELIQUIS is required\(^2\)
ELIQUIS® (apixaban): CONSIDERATIONS FOR REVERSING THE ANTICOAGULANT EFFECTS¹

An agent to reverse the anti-factor Xa activity of ELIQUIS is available

- Please visit www.andexxa.com for more information on availability of a reversal agent

The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, ie, for about two drug half lives

(Content continues on next page)
Additional information for reversal of anticoagulant effect

- Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies
- When PCCs are used, monitoring for the anticoagulation effect of ELIQUIS using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended
- Hemodialysis does not appear to have a substantial impact on ELIQUIS exposure
- Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of ELIQUIS
- There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving ELIQUIS
- There is no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving ELIQUIS, and they are not expected to be effective as a reversal agent

Activated oral charcoal reduces absorption of ELIQUIS, thereby lowering ELIQUIS plasma concentration

aPTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time.

Please see attached Full U.S. Prescribing Information, including Boxed WARNINGS, and Medication Guide.
CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS® (apixaban) (e.g., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- 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.
WARNINGS AND PRECAUTIONS

• **Bleeding Risk:** ELIQUIS® (apixaban) increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

  o Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.

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

  o The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.
• Spinal/Epidural Anesthesia or Puncture:
  Patients treated with ELIQUIS® (apixaban) undergoing spinal/epidural anesthesia or puncture may develop 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 and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.
• **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS® (apixaban) have not been studied in patients with prosthetic heart valves and is not recommended in these patients.

• **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.

• **Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome (APS):** Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive APS. For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Please see additional Important Safety Information continued on next page.
Please see attached Full U.S. Prescribing Information, including **Boxed WARNINGS**, and Medication Guide.
ADVERSE REACTIONS

• The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

• ELIQUIS® (apixaban) 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 noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

• Combined P-gp and Strong CYP3A4 Inhibitors: Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving
ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS® (apixaban) with combined P-gp and strong CYP3A4 inhibitors.

**Clarithromycin**
Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

- **Combined P-gp and Strong CYP3A4 Inducers:** Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) because such drugs will decrease exposure to apixaban.

- **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.

PREGNANCY

- The limited available data on ELIQUIS® (apixaban) use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery, and in the fetus and neonate.

  - Labor or delivery: ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches.

LACTATION

- Breastfeeding is not recommended during treatment with ELIQUIS.
FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

- Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician. The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including ELIQUIS® (apixaban) should be assessed in these patients and those with abnormal uterine bleeding.
ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

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.

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


Please see additional Important Safety Information throughout. Please see attached Full U.S. Prescribing Information, including Boxed WARNINGS, and Medication Guide.
ELIQUIS® (apixaban) tablets, for oral use

Initial U.S. Approval: 2012

WARNINGS AND PRECAUTIONS

• Premature discontinuation of ELIQUIS increases the risk of thrombotic events.

(B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning.

WARNINGS AND PRECAUTIONS

• Premature discontinuation of ELIQUIS increases the risk of thrombotic events:

1. DOSEAGE FORMS AND STRENGTHS

• Tablets: 2.5 mg and 5 mg

2. CONTRAINDICATIONS

• Active pathological bleeding

7. DRUG INTERACTIONS

• Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban. Reduce ELIQUIS dose or avoid coadministration. (2.4, 5.1.14.1)

14.3 Treatment of DVT and PE and Reduction in the Risk of

• Prophylaxis of DVT following hip or knee replacement surgery:
• The recommended dose is 2.5 mg orally twice daily. (2.1)
• Treatment of DVT and PE:
• The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)
• Reduction in the risk of recurrent DVT and PE following initial therapy:
• The recommended dose is 2.5 mg taken orally twice daily. (2.1)

• Tablets: 2.5 mg and 5 mg

• Reduction in the 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)

1. INDICATIONS AND USAGE

• ELIQUIS is a factor Xa inhibitor indicated:

1. PROPHYLAXIS OF DEEP VEIN THROMBOSIS FOLLOWING HIP OR KNEE REPLACEMENT SURGERY

• Treatment of DVT and PE:

• Prophylaxis of DVT following hip or knee replacement surgery:

• Reduction in the risk of recurrent DVT and PE following initial therapy:

• Tablets: 2.5 mg and 5 mg

• The recommended dose is 2.5 mg orally twice daily. (2.1)

• The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)

1. INDICATIONS AND USAGE

• to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. (1.1)

3. DOSAGE FORMS AND STRENGTHS

• 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. (1.3.14.1)

4. CONTRAINDICATIONS

• Severe hypersensitivity to ELIQUIS (apixaban) (4)

5. WARNINGS AND PRECAUTIONS

• Active pathological bleeding (4)

10. OVERDOSAGE

• Severe hypersensitivity to ELIQUIS (apixaban) (4)

13. NONCLINICAL TOXICOLOGY

• ELIQUIS can cause serious, potentially fatal, bleeding. Promptly evaluate signs and symptoms of blood loss. An agent to reverse the anti-factor Xa activity of apixaban is available. (5.2)

• Prophylaxis of DVT following hip or knee replacement surgery:
• The recommended dose is 2.5 mg orally twice daily. (2.1)
• Treatment of DVT and PE:
• The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)
• Reduction in the risk of recurrent DVT and PE following initial therapy:
• The recommended dose is 2.5 mg taken orally twice daily. (2.1)

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.

DRUG INTERACTIONS

• ELIQUIS can cause serious, potentially fatal, bleeding. Promptly evaluate signs and symptoms of blood loss. An agent to reverse the anti-factor Xa activity of apixaban is available. (5.2)

• Prophylaxis of DVT following hip or knee replacement surgery:

• Tablets: 2.5 mg and 5 mg

• Prophylaxis of DVT following hip or knee replacement surgery:

• Tablets: 2.5 mg and 5 mg

• The recommended dose is 2.5 mg orally twice daily. (2.1)

• The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)

• The recommended dose is 2.5 mg taken orally twice daily. (2.1)

• Tablets: 2.5 mg and 5 mg

• Reduction in the risk of recurrent DVT and PE following initial therapy:

• Tablets: 2.5 mg and 5 mg

• Prophylaxis of DVT following hip or knee replacement surgery:

• The recommended dose is 2.5 mg orally twice daily. (2.1)

• The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)

• The recommended dose is 2.5 mg taken orally twice daily. (2.1)

• Tablets: 2.5 mg and 5 mg

• Prophylaxis of DVT following hip or knee replacement surgery:

• The recommended dose is 2.5 mg orally twice daily. (2.1)

• The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)

• The recommended dose is 2.5 mg taken orally twice daily. (2.1)

• Tablets: 2.5 mg and 5 mg

• Prophylaxis of DVT following hip or knee replacement surgery:

• The recommended dose is 2.5 mg orally twice daily. (2.1)

• The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)

• The recommended dose is 2.5 mg taken orally twice daily. (2.1)

• Tablets: 2.5 mg and 5 mg

• Prophylaxis of DVT following hip or knee replacement surgery:

• The recommended dose is 2.5 mg orally twice daily. (2.1)

• The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)

• The recommended dose is 2.5 mg taken orally twice daily. (2.1)

• Tablets: 2.5 mg and 5 mg

• Prophylaxis of DVT following hip or knee replacement surgery:

• The recommended dose is 2.5 mg orally twice daily. (2.1)

• The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)

• The recommended dose is 2.5 mg taken orally twice daily. (2.1)

• Tablets: 2.5 mg and 5 mg
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.

2.2 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.

2.3 Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptably high bleeding risk. If ELIQUIS is discontinued at least 24 hours prior to elective surgery or invasive procedures, the dose should be resumed immediately after surgery or invasive procedures. If ELIQUIS is administered 24 to 48 hours after stopping ELIQUIS and prior to the intervention, the dose should be increased to the daily dose at the time of the next dose of ELIQUIS.

2.4 Converting from or to ELIQUIS

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

Switching from ELIQUIS to warfarin:
ELIQUIS affects INR, so that initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue ELIQUIS and begin both a parental 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 from ELIQUIS to anticoagulants other than warfarin (oral or parenteral):
Discontinue ELIQUIS and begin taking the new anticoagulant other than warfarin at the usual time of the next dose of ELIQUIS.

Switching from anticoagulants other than warfarin (oral or parenteral) to ELIQUIS:
Discontinue the anticoagulant other than warfarin and begin taking ELIQUIS at the usual time of the next dose of the anticoagulant other than warfarin.

2.5 Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose by 50% when ELIQUIS is coadministered with drugs that are combined P-glycoprotein (P-gp) and strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, itraconazole, ritonavin) [see Clinical Pharmacology (12.3)].

In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors [see Drug Interactions (7.1)].

2.6 Administration Options

For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS tablets may be crushed and suspended in water, 5% dextrose in water (DSW), or apple juice, or mixed with applesauce and promptly administered orally [see Clinical Pharmacology (12.3)]. Alternatively, ELIQUIS tablets may be crushed and suspended in 60 mL of water or DSW and promptly delivered through a nasogastric tube [see Clinical Pharmacology (12.3)].

Crushed ELIQUIS tablets are stable in water, DSW, apple juice, and applesauce for up to 4 hours.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of 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 signs and symptoms 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**

An agent to reverse the anti-factor Xa activity of apixaban is available. 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. Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be considered, but have 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)].

Hemodialysis 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) in individuals receiving ELIQUIS, 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, or 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 require thrombolysis or pulmonary embolectomy.

### 5.6 Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

### 6 ADVERSE REACTIONS

The following clinically significant 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.

---

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

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS N=9088</th>
<th>Warfarin N=9052</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial (ICH)²</td>
<td>52 (0.33)</td>
<td>125 (0.82)</td>
<td>0.41 (0.30, 0.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemorrhagic stroke³</td>
<td>38 (0.24)</td>
<td>74 (0.49)</td>
<td>0.51 (0.34, 0.75)</td>
<td></td>
</tr>
<tr>
<td>Other ICH</td>
<td>15 (0.10)</td>
<td>51 (0.34)</td>
<td>0.29 (0.16, 0.51)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal (GI)</td>
<td>128 (0.83)</td>
<td>141 (0.93)</td>
<td>0.89 (0.70, 1.14)</td>
<td></td>
</tr>
<tr>
<td>Fatal**</td>
<td>10 (0.06)</td>
<td>37 (0.24)</td>
<td>0.27 (0.13, 0.53)</td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>4 (0.03)</td>
<td>30 (0.20)</td>
<td>0.13 (0.05, 0.37)</td>
<td></td>
</tr>
<tr>
<td>Non-intracranial</td>
<td>6 (0.04)</td>
<td>7 (0.05)</td>
<td>0.84 (0.28, 2.15)</td>
<td></td>
</tr>
</tbody>
</table>

* 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).

² 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, intrapleural, vascular, intracardiac, intracranial and subarachnoid bleeding.

³ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid hemorrhage.

**Fatal bleeding is an adjudicated death with the primary cause of death as intracranial major bleed.

On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.

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

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, CHADS2 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 ELIQUIS with diabetes bled more (3% per year) than did subjects without diabetes (1.9% per year).
Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ELIQUIS</th>
<th>Aspirin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>45 (1.41)</td>
<td>29 (0.92)</td>
<td>1.54 (0.96, 2.45)</td>
<td>0.07</td>
</tr>
<tr>
<td>Fatal</td>
<td>5 (0.16)</td>
<td>5 (0.16)</td>
<td>0.99 (0.23, 4.29)</td>
<td>-</td>
</tr>
<tr>
<td>Intracranial</td>
<td>11 (0.34)</td>
<td>11 (0.35)</td>
<td>0.99 (0.39, 2.51)</td>
<td>-</td>
</tr>
</tbody>
</table>

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

Other Adverse Reactions

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

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

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

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

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

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

<table>
<thead>
<tr>
<th>Bleeding Endpoint*</th>
<th>ADVANCE-3</th>
<th>ADVANCE-2</th>
<th>ADVANCE-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Replacement Surgery</td>
<td>ELIQUIS 2.5 mg po bid 35±3 days</td>
<td>Enoxaparin 40 mg sc 35±3 days</td>
<td>ELIQUIS 2.5 mg po bid 12±2 days</td>
</tr>
<tr>
<td>Knee Replacement Surgery</td>
<td>Enoxaparin 40 mg sc 12±2 days</td>
<td>ELIQUIS 2.5 mg po bid 12±2 days</td>
<td>Enoxaparin 30 mg sc q12h 12±2 days</td>
</tr>
<tr>
<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>
<td>First dose 12 to 24 hours post surgery</td>
</tr>
</tbody>
</table>

All treated N=2673 N=2659 N=1501 N=1508 N=1596 N=1588

Major (including surgical site) | 22 (0.82%) | 18 (0.68%) | 9 (0.60%) | 14 (0.93%) | 11 (0.69%) | 22 (1.39%) |

Fatal | 0 | 0 | 0 | 0 | 1 (0.06%) |

Hgb decrease ≥2 g/dL | 13 (0.49%) | 10 (0.38%) | 8 (0.53%) | 9 (0.60%) | 10 (0.63%) | 16 (1.01%) |

Transfusion of ≥2 units RBC | 16 (0.60%) | 14 (0.53%) | 5 (0.33%) | 9 (0.60%) | 9 (0.56%) | 18 (1.13%) |

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

<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>ELIQUIS 2.5 mg po bid 35±3 days</td>
<td>Enoxaparin 40 mg sc qd 35±3 days</td>
<td>ELIQUIS 2.5 mg po bid 12±2 days</td>
<td>Enoxaparin 40 mg sc qd 12±2 days</td>
</tr>
<tr>
<td>First dose 12 to 24 hours post surgery</td>
<td>First dose 9 to 15 hours post surgery</td>
<td>First dose 9 to 15 hours post surgery</td>
<td>First dose 12 to 24 hours post surgery</td>
</tr>
<tr>
<td>Bleed at critical site§</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>2 (0.13%)</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 ELIQUIS (administered 12 to 24 hours post-surgery).

‡Includes 5 subjects with major bleeding events that occurred before the first dose of ELIQUIS (administered 12 to 24 hours post-surgery).

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

¶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 Treated for DVT and PE in the AMPLIFY Study

<table>
<thead>
<tr>
<th>Reaction</th>
<th>ELIQUIS, n (%)</th>
<th>Enoxaparin/Warfarin, n (%)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>49 (1.8)</td>
<td>40 (1.6)</td>
<td>0.31 (0.17, 0.55)</td>
</tr>
<tr>
<td>Minor</td>
<td>261 (9.7)</td>
<td>505 (18.8)</td>
<td>0.17 (0.10, 0.3)</td>
</tr>
<tr>
<td>All</td>
<td>676 (25.1)</td>
<td>215 (8.0)</td>
<td>0.07 (0.04, 0.13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reaction</th>
<th>ELIQUIS, n (%)</th>
<th>Enoxaparin/Warfarin, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>159 (2.7)</td>
<td>159 (2.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>178 (3.0)</td>
<td>178 (3.0)</td>
</tr>
<tr>
<td>Contusion</td>
<td>115 (1.9)</td>
<td>115 (1.9)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>81 (1.4)</td>
<td>81 (1.4)</td>
</tr>
<tr>
<td>Postprocedural hemorrhage</td>
<td>60 (1.0)</td>
<td>60 (1.0)</td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>71 (1.2)</td>
<td>71 (1.2)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>69 (1.2)</td>
<td>69 (1.2)</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>65 (1.1)</td>
<td>65 (1.1)</td>
</tr>
</tbody>
</table>

Less common adverse reactions in ELIQUIS-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), hepatobilia
- 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>Reaction</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>Minor</td>
<td>115 (4.3)</td>
<td>261 (9.7)</td>
<td>0.17 (0.10, 0.3)</td>
</tr>
<tr>
<td>All</td>
<td>102 (3.7)</td>
<td>667 (25.1)</td>
<td>0.07 (0.04, 0.13)</td>
</tr>
</tbody>
</table>

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

AMPLIFY-EXT 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 1417 (5.6%) 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.

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

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

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.
ELIQUIS® (apixaban)

Table 7: Bleeding Results in the AMPLIFY-EXT Study

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS 2.5 mg bid N=840 n (%)</th>
<th>ELIQUIS 5 mg bid N=811 n (%)</th>
<th>Placebo N=826 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>CRNM*</td>
<td>25 (3.0)</td>
<td>34 (4.2)</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td>Major + CRNM</td>
<td>27 (3.2)</td>
<td>35 (4.3)</td>
<td>22 (2.7)</td>
</tr>
<tr>
<td>Minor</td>
<td>75 (8.9)</td>
<td>98 (12.1)</td>
<td>58 (7.0)</td>
</tr>
<tr>
<td>All</td>
<td>94 (11.2)</td>
<td>121 (14.9)</td>
<td>74 (9.0)</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.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS 2.5 mg bid N=840 n (%)</th>
<th>ELIQUIS 5 mg bid N=811 n (%)</th>
<th>Placebo N=826 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>13 (1.5)</td>
<td>29 (3.6)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>12 (1.4)</td>
<td>17 (2.1)</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>13 (1.5)</td>
<td>16 (2.0)</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>Confusion</td>
<td>18 (2.1)</td>
<td>18 (2.2)</td>
<td>18 (2.2)</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>12 (1.4)</td>
<td>9 (1.1)</td>
<td>3 (0.4)</td>
</tr>
</tbody>
</table>

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

- Blood and lymphatic system disorders: hemorrhagic anemia
- Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage
- Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma
- Musculoskeletal and connective tissue disorders: muscle hemorrhage
- Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menomethrombria, genital hemorrhage
- Vascular disorders: hemorrhage
- Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae
- Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage
- Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

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 and other thromboembolic events.

7.1 Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)].

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with combined P-gp and strong CYP3A4 inhibitors [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)].

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS [see Clinical Pharmacology (12.3)].

7.2 Combined P-gp and Strong CYP3A4 Inducers

Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (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 antplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2: a placebo-controlled clinical trial of ELIQUIS 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 ELIQUIS compared to placebo. The rate of ISTH major bleeding was 2.6% per year with ELIQUIS versus 0.6% per year with placebo in patients receiving single antplatelet therapy and was 5.9% per year with ELIQUIS versus 2.5% per year with placebo in those receiving dual antplatelet 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 antplatelet therapy with ELIQUIS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery. In animal reproduction studies, no adverse developmental effects were seen when apixaban was administered to rats (orally), rabbits (intravenously) and mice (orally) during organogenesis at unbound apixaban exposure levels up to 4, 1 and 19 times, respectively, the human exposure based on area under plasma-concentration time curve (AUC) at the Maximum Recommended Human Dose (MRHD) of 5 mg twice daily.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

- Disease-associated maternal and/or embryo/fetal risk

Pregnancy confers an increased risk of thromboembolism that is higher for women with underlying thromboembolic disease and certain high-risk pregnancy conditions. Published data describe that women with a previous history of venous thrombosis are at high risk for recurrence during pregnancy.

- Fetal/Neonatal adverse reactions

Use of anticoagulants, including ELIQUIS, may increase the risk of bleeding in the fetus and neonate.

- Labor or delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches [see Warnings and Precautions (5.3)].

Data

Animal Data

No developmental toxicities were observed when apixaban was administered during organogenesis to rats (orally), rabbits (intravenously) and mice (orally) at unbound apixaban exposure levels 4, 1, and 19 times, respectively, the human exposures at the MRHD. There was no evidence of fetal bleeding, although conceptus exposure was confirmed in rats and rabbits. Oral administration of apixaban to rat dams from gestation day 6 through lactation day 21 at maternal unbound apixaban exposures ranging from 1.4 to 5 times the human exposures at the MRHD was not associated with reduced maternal mortality or reduced conceptus/neonatal viability, although increased incidences of peri-vaginal bleeding were observed in dams at all doses. There was no evidence of neonatal bleeding.

8.2 Lactation

Risk Summary

There are no data on the presence of apixaban or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Apixaban and/or its metabolites were present in the milk of rats (see Data). Because human exposure through milk is unknown, breastfeeding is not recommended during treatment with ELIQUIS.

Data

Animal Data

Maximal plasma concentrations were observed after 30 minutes following a single oral administration of a 5 mg dose to lactating rats. Maximal milk concentrations were observed 6 hours after dosing. The milk to plasma AUC (0-24) ratio is 30:1 indicating that apixaban can accumulate in milk. The concentrations of apixaban in animal milk does not necessarily predict the concentration of drug in human milk.
ELIQUIS® (apixaban)

8.3 Females and Males of Reproductive Potential
Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including ELIQUIS should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

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

8.5 Geriatric Use
Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 years of age and older, and >31% were 75 years of age and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 years of age and older, while 16% were 75 years of age and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 years of age and older and >13% were 75 years of age 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 60 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 usually 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 (12.2)]. 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.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE
No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis [see Dosage and Administration (2.1)]. Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment
No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A).

Because patients with moderate hepatic impairment (Child-Pugh class B) 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 (Child-Pugh class C) [see Clinical Pharmacology (12.2)].

10 OVERDOSE
Overdose of ELIQUIS increases the risk of bleeding [see Warnings and Precautions (5.2)].

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

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of ELIQUIS overdose or accidental ingestion. An agent to reverse the anti-factor Xa activity of apixaban is available.

11 DESCRIPTION
ELIQUIS (apixaban), a factor Xa (FXa) inhibitor, is chemically described as 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide. Its molecular formula is C_{26}H_{29}N_{4}O_{6}, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:

![Structural formula of apixaban]

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 tablet) or red iron oxide (5 mg tablets).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Apixaban is a selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXas, 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 anticoagulant 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.

Effect of PCGs on Pharmacodynamics of ELIQUIS
There is no clinical experience to reverse bleeding with the use of 4-factor PC products in individuals who have received ELIQUIS.

Effects of 4-factor PCGs on the pharmacodynamics of apixaban were studied in healthy subjects. Following administration of apixaban dosed to steady state, endogenous thrombin potential (ETP) returned to pre-apixaban levels 4 hours after the initiation of a 30-minute PCC infusion, compared to 45 hours with placebo. Mean ETP levels continued to increase and exceeded pre-apixaban levels reaching a maximum (34%-51% increase over pre-apixaban levels) at 21 hours after initiating PCC and remained elevated (21%-27% increase) at the end of the study (69 hours after initiation of PCC). The clinical relevance of this increase in ETP is unknown.

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

Specific Populations

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

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

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

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

Absorption

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg of ELIQUIS. Food does not affect the bioavailability of apixaban. Maximum concentrations (Cmax) of apixaban appear 3 to 4 hours after oral administration of ELIQUIS. At doses ≥25 mg, apixaban displays dissolution-limited absorption with decreased bioavailability. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was similar to that after oral administration of 2 intact 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets mixed with 30 g of applesauce, the Cmax and AUC were 20% and 16% lower, respectively, when compared to administration of 2 intact 5 mg tablets. Following administration of a crushed 5 mg ELIQUIS tablet that was suspended in 60 mL DSW and delivered through a nasogastric tube, exposure was similar to that seen in other clinical trials involving healthy volunteers receiving a single oral 5 mg tablet dose.

Distribution

Plasma protein binding in humans is approximately 87%. The volume of distribution (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, CYP2B, CYP2C19, and CYP2J2. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Unchanged apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.

Elimination

Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces. Apixaban has a total clearance of approximately 3.3 L/hour and an apparent half-life of approximately 12 hours following oral administration.

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

Drug Interaction Studies

In 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 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>Cmax</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined P-gp and Strong CYP3A4 Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole 400 mg</td>
<td>Cmax</td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin 500 mg</td>
<td>Cmax</td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Other CYP3A4 and P-gp Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem 360 mg</td>
<td>Cmax</td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Naproxen 500 mg</td>
<td>Cmax</td>
<td>AUC</td>
<td></td>
</tr>
<tr>
<td>Combined P-gp and Strong CYP3A4 Inducer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin 600 mg</td>
<td>Cmax</td>
<td>AUC</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Specific Populations

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

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

<table>
<thead>
<tr>
<th>Population Description</th>
<th>PK</th>
<th>AUC</th>
<th>AUC</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-Stage Renal</td>
<td>Cmax</td>
<td>No dose adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease*</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Impairment:</td>
<td>Cmax</td>
<td>No dose adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe/Normal</td>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Impairment:</td>
<td>Cmax</td>
<td>No dose adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/Normal</td>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Impairment:</td>
<td>Cmax</td>
<td>No dose adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/Normal</td>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age:</td>
<td>Cmax</td>
<td>No dose adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65 years/18-40 years</td>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight:</td>
<td>Cmax</td>
<td>No dose adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥120 kg/65-85 kg</td>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight:</td>
<td>Cmax</td>
<td>No dose adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 kg/65-85 kg</td>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment:</td>
<td>Cmax</td>
<td>Dosing recommendation cannot be provided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/Normal</td>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment:</td>
<td>Cmax</td>
<td>No dose adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/Normal</td>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 was 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.
Apixaban was neither mutagenic in the bacterial reverse mutation (Ames) test, nor clastogenic in Chinese hamster ovary cells in vitro, in a 1-month in vivo cytogenetic assay in rat peripheral blood lymphocytes, or in a rat micronucleus test. Apixaban had no effect on fertility in male or female rats when administered to female rats at doses up to 1000 mg/kg/day from implantation through the end of lactation, producing no adverse findings in male offspring (F1 generation) at doses up to 1000 mg/kg/day, a dose resulting in exposure to unbound apixaban that is 5 times the human exposure. Adverse effects in the male offspring were limited to decreased mating and fertility indices at a dose resulting in exposure unbound apixaban that is ≥5 times the human exposure.

**STUDIES**

### Ion of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

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 embolism. In ARISTOTLE, patients were randomized to ELIQUIS (5 mg twice daily) or warfarin (targeted to an INR range of 2.0-3.0). Patients had to have one or more 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) or to one of several subgroups defined by additional risk factors for stroke:

- Transient ischemic attack (TIA)
- Embolism
- Than or equal to 75 years
- Tension requiring treatment
- N New York Heart Association Class 2
- Ejection fraction ≤40%

The primary objective of ARISTOTLE was to determine whether ELIQUIS 5 mg twice daily (or 2.5 mg twice daily in subjects with at least 2 of 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) or to one of the subgroups defined by additional risk factors for stroke, had a lower risk of stroke (ischemic or hemorrhagic) and systemic embolism. Superiority of ELIQUIS over warfarin for the primary endpoint was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic and systemic embolism (Table 9 and Figure 4). Superiority to warfarin was primarily due to significantly fewer major bleeds than warfarin [see Adverse

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

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS N=9120</th>
<th>Warfarin N=9081</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>212 (1.27)</td>
<td>265 (1.60)</td>
<td>0.79 (0.66, 0.96)</td>
</tr>
<tr>
<td>Stroke</td>
<td>199 (1.19)</td>
<td>250 (1.51)</td>
<td>0.79 (0.65, 0.96)</td>
</tr>
<tr>
<td>Ischemic without hemorrhage</td>
<td>140 (0.83)</td>
<td>136 (0.82)</td>
<td>1.02 (0.81, 1.30)</td>
</tr>
<tr>
<td>Ischemic with hemorrhagic conversion</td>
<td>12 (0.07)</td>
<td>20 (0.12)</td>
<td>0.60 (0.29, 1.06)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>40 (0.24)</td>
<td>78 (0.47)</td>
<td>0.51 (0.35, 0.75)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (0.08)</td>
<td>21 (0.13)</td>
<td>0.65 (0.33, 1.31)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>15 (0.09)</td>
<td>17 (0.10)</td>
<td>0.87 (0.44, 1.73)</td>
</tr>
</tbody>
</table>

The primary endpoint was based on the time to first event (one per subject) across most major subgroups including weight, CHADS2 score (a scale from 0 to 6 used to predict risk of stroke in patients with AF), with higher scores predictive of higher risk, prior warfarin use, level of renal impairment, geographic region, an randomization (Figure 5).
### Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Apixaban</th>
<th>Warfarin</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>
<td>0.79 (0.66, 0.95)</td>
</tr>
<tr>
<td>Prior Warfarin/VKA Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experienced (57%)</td>
<td>102 / 5208 (1.1)</td>
<td>138 / 5193 (1.5)</td>
<td>0.73 (0.57, 0.95)</td>
</tr>
<tr>
<td>Naive (43%)</td>
<td>110 / 3912 (1.3)</td>
<td>127 / 3888 (1.8)</td>
<td>0.86 (0.66, 1.11)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 (30%)</td>
<td>51 / 2731 (1.0)</td>
<td>44 / 2740 (0.9)</td>
<td>1.16 (0.77, 1.73)</td>
</tr>
<tr>
<td>≥65 and &lt;75 (39%)</td>
<td>82 / 3539 (1.3)</td>
<td>112 / 3513 (1.7)</td>
<td>0.72 (0.54, 0.96)</td>
</tr>
<tr>
<td>≥75 (31%)</td>
<td>79 / 2850 (1.6)</td>
<td>109 / 2828 (2.2)</td>
<td>0.71 (0.53, 0.95)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (65%)</td>
<td>132 / 5886 (1.2)</td>
<td>160 / 5899 (1.5)</td>
<td>0.82 (0.65, 1.04)</td>
</tr>
<tr>
<td>Female (35%)</td>
<td>80 / 3234 (1.3)</td>
<td>105 / 3182 (1.8)</td>
<td>0.74 (0.56, 1.00)</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 kg (11%)</td>
<td>34 / 1018 (2.0)</td>
<td>52 / 967 (3.2)</td>
<td>0.63 (0.41, 0.97)</td>
</tr>
<tr>
<td>&gt;60 kg (89%)</td>
<td>177 / 8070 (1.2)</td>
<td>212 / 8084 (1.4)</td>
<td>0.83 (0.68, 1.01)</td>
</tr>
<tr>
<td>Prior Stroke or TIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (19%)</td>
<td>73 / 1694 (2.5)</td>
<td>98 / 1742 (3.2)</td>
<td>0.76 (0.56, 1.03)</td>
</tr>
<tr>
<td>No (81%)</td>
<td>139 / 7426 (1.0)</td>
<td>167 / 7339 (1.2)</td>
<td>0.82 (0.65, 1.03)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (25%)</td>
<td>57 / 2284 (1.4)</td>
<td>75 / 2263 (1.9)</td>
<td>0.75 (0.53, 1.05)</td>
</tr>
<tr>
<td>No (75%)</td>
<td>155 / 6836 (1.2)</td>
<td>190 / 6818 (1.5)</td>
<td>0.81 (0.65, 1.00)</td>
</tr>
<tr>
<td>CHADS2 Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 (34%)</td>
<td>44 / 3100 (0.7)</td>
<td>51 / 3083 (0.9)</td>
<td>0.85 (0.57, 1.27)</td>
</tr>
<tr>
<td>2 (36%)</td>
<td>74 / 3262 (1.2)</td>
<td>82 / 3254 (1.4)</td>
<td>0.90 (0.66, 1.23)</td>
</tr>
<tr>
<td>≥3 (30%)</td>
<td>94 / 2758 (2.0)</td>
<td>132 / 2744 (2.8)</td>
<td>0.70 (0.54, 0.91)</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 mL/min (1%)</td>
<td>6 / 137 (2.8)</td>
<td>10 / 133 (5.1)</td>
<td>0.55 (0.20, 1.53)</td>
</tr>
<tr>
<td>30-50 mL/min (15%)</td>
<td>48 / 1365 (2.0)</td>
<td>59 / 1382 (2.5)</td>
<td>0.83 (0.57, 1.21)</td>
</tr>
<tr>
<td>&gt;50-80 mL/min (42%)</td>
<td>87 / 3817 (1.2)</td>
<td>116 / 3770 (1.7)</td>
<td>0.74 (0.56, 0.97)</td>
</tr>
<tr>
<td>&gt;80 mL/min (41%)</td>
<td>70 / 3761 (1.0)</td>
<td>79 / 3757 (1.1)</td>
<td>0.88 (0.64, 1.21)</td>
</tr>
<tr>
<td>Geographic Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US (19%)</td>
<td>31 / 1720 (0.9)</td>
<td>39 / 1697 (1.2)</td>
<td>0.79 (0.50, 1.27)</td>
</tr>
<tr>
<td>Non-US (81%)</td>
<td>181 / 7400 (1.3)</td>
<td>226 / 7384 (1.7)</td>
<td>0.79 (0.65, 0.96)</td>
</tr>
<tr>
<td>Aspirin at Randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (31%)</td>
<td>70 / 2859 (1.3)</td>
<td>94 / 2773 (1.9)</td>
<td>0.72 (0.53, 0.98)</td>
</tr>
<tr>
<td>No (69%)</td>
<td>142 / 6261 (1.2)</td>
<td>171 / 6308 (1.5)</td>
<td>0.83 (0.67, 1.04)</td>
</tr>
</tbody>
</table>

The above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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)].

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ELIQUIS N=2807</th>
<th>Aspirin N=2791</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>51 (1.62)</td>
<td>113 (3.63)</td>
<td>0.45 (0.32, 0.62)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic or undetermined</td>
<td>43 (1.37)</td>
<td>97 (3.11)</td>
<td>0.44 (0.31, 0.63)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>6 (0.19)</td>
<td>9 (0.28)</td>
<td>0.67 (0.24, 1.88)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>2 (0.06)</td>
<td>13 (0.41)</td>
<td>0.15 (0.03, 0.68)</td>
</tr>
<tr>
<td>MI</td>
<td>24 (0.76)</td>
<td>28 (0.89)</td>
<td>0.86 (0.50, 1.48)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>111 (3.51)</td>
<td>140 (4.42)</td>
<td>0.79 (0.62, 1.02)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>84 (2.65)</td>
<td>96 (3.03)</td>
<td>0.87 (0.65, 1.17)</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 patients undergoing elective knee replacement surgery, ELIQUIS 2.5 mg orally twice daily was compared to enoxaparin 40 mg subcutaneously once daily (ADVANCE-2, N=3057) or enoxaparin 30 mg subcutaneously every 12 hours (ADVANCE-1, N=3195). In the ADVANCE-2 study, the first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. In the ADVANCE-1 study, both ELIQUIS and enoxaparin were initiated 12 to 24 hours post surgery. Treatment duration in both ADVANCE-2 and ADVANCE-1 was 10 to 14 days.

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

The efficacy data are provided in Tables 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>Event</th>
<th>ADVANCE-3</th>
<th>ADVANCE-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>N=1949</td>
<td>N=1917</td>
</tr>
<tr>
<td><strong>Total VTE/All-cause death</strong></td>
<td>27 (1.39%)</td>
<td>74 (3.86%)</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>3 (0.11%)</td>
<td>1 (0.04%)</td>
</tr>
<tr>
<td><strong>PE</strong></td>
<td>3 (0.11%)</td>
<td>5 (0.19%)</td>
</tr>
<tr>
<td><strong>Symptomatic DVT</strong></td>
<td>1 (0.04%)</td>
<td>5 (0.19%)</td>
</tr>
<tr>
<td><strong>Number of Patients</strong></td>
<td>N=2196</td>
<td>N=2190</td>
</tr>
<tr>
<td><strong>Proximal DVT</strong></td>
<td>7 (0.32%)</td>
<td>20 (0.91%)</td>
</tr>
<tr>
<td><strong>Number of Patients</strong></td>
<td>N=1951</td>
<td>N=1908</td>
</tr>
<tr>
<td><strong>Distal DVT</strong></td>
<td>20 (1.03%)</td>
<td>57 (2.99%)</td>
</tr>
</tbody>
</table>

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

ELIQUIS® (apixaban)

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 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).

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

<table>
<thead>
<tr>
<th>Event</th>
<th>ADVANCE-1</th>
<th>ADVANCE-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>N=1157</td>
<td>N=1130</td>
</tr>
<tr>
<td><strong>Total VTE/All-cause death</strong></td>
<td>104 (8.9%)</td>
<td>100 (8.8%)</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>3 (0.19%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>PE</strong></td>
<td>16 (1.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Symptomatic DVT</strong></td>
<td>3 (0.19%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

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

† Includes symptomatic and asymptomatic DVT.

‡ Includes symptomatic and asymptomatic DVT.
study, patients were stratified according to their index event of PE (DVT or PE) or DVT (without PE). Efficacy in the initial treatment of VTE was examined in the two subgroups.

I have 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. 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.

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. In the AMPLIFY-EXT study, patients with either an unprovoked DVT or PE were included. In patients who had had multiple episodes of unprovoked DVT or PE were excluded from the study.

The AMPLIFY-EXT study enrolled patients with either an unprovoked DVT or PE at baseline, and then randomized patients to receive placebo or ELIQUIS 2.5 mg or 5 mg orally twice daily for 12 months. The mean age in the AMPLIFY-EXT study was 57 years. The study population was Caucasian, 5% Asian, and 3% Black.

In the AMPLIFY-EXT study, both doses of ELIQUIS were superior to placebo in the primary endpoint of symptomatic, recurrent VTE (nonfatal DVT or PE), or all-cause death (Table 14).

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>d death*</td>
<td>59 (2.3%)</td>
<td>71 (2.7%)</td>
<td>0.84 (0.60, 1.18)</td>
</tr>
<tr>
<td>22 (0.8%)</td>
<td>35 (1.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 (1.0%)</td>
<td>25 (0.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i⁹th†</td>
<td>12 (0.4%)</td>
<td>16 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>death</td>
<td>84 (3.2%)</td>
<td>104 (4.0%)</td>
<td>0.82 (0.61, 1.08)</td>
</tr>
<tr>
<td>l death</td>
<td>61 (2.3%)</td>
<td>77 (2.9%)</td>
<td>0.80 (0.57, 1.11)</td>
</tr>
</tbody>
</table>

* Noninferior compared to enoxaparin/warfarin (P-value <0.0001).
† 12 (0.4%) 16 (0.6%)
‡ 22 (0.8%) 25 (0.9%)
§ 61 (2.3%) 77 (2.9%)
¶ 59 (2.3%) 71 (2.7%)
# 22 (0.8%) 35 (1.3%)
$ 27 (1.0%) 25 (0.9%)
<table>
<thead>
<tr>
<th>Tablet</th>
<th>Strength</th>
<th>Color/Shape</th>
<th>Markings</th>
<th>Package Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
<td>Yellow, round, biconvex</td>
<td>Debossed with “893” on one side and “2½” on the other side</td>
<td>Bottles of 60 Hospital Unit-Dose Blister Package of 100</td>
<td></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 Hospital Unit-Dose Blister Package of 100</td>
<td></td>
</tr>
</tbody>
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Storage and Handling
Store at 20°C to 25°C (68°F-77°F); excursions permitted between 1 (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION
Advise patients to read the FDA-approved patient labeling (Medication Guide) before any new drug is taken.
- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and if bleeding more easily when treated with ELIQUIS. Advise patients to watch for signs and symptoms of hypovolemia and of the urgent need to report any unusual bleeding.
- To tell their physicians and dentists they are taking ELIQUIS, or product known to affect bleeding (including nonprescription products, aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled.
- If the patient is having neuraxial anesthesia or spinal puncture, inf to watch for signs and symptoms of spinal or epidural hematomas and Precautions (5.3). If any of these symptoms occur, advise the emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or intend to breastfeed during treatment with ELIQUIS. If breastfeeding or intend to breastfeed during treatment with ELIQUIS.
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube and Precautions (5.3) [see Warnings and Precautions (5.3)].
- To what do if a dose is missed.

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ELIQUIS® (apixaban)

MEDICATION GUIDE
ELIQUIS® (ELL eh kwiss)
apixaban)tablets

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

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

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

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

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

  You may have a higher risk of bleeding if you take ELIQUIS and take other medicines that increase
  your risk of bleeding, including:
  • aspirin or aspirin-containing products
  • long-term (chronic) use of nonsteroidal anti-inflammatory drugs (NSAIDs)
  • warfarin sodium (COUMADIN®, 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® (apixaban)

- **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.

- **ELIQUIS is not for use in people with antiphospholipid syndrome (APS), especially with positive triple antibody testing, who have a history of blood clots.**

**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 antiphospholipid syndrome
- 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?”
ELIQUIS® (apixaban)

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.
**ELIQUIS® (apixaban)**

**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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