Dosing Guide for All ELIQUIS Indications

Find out more at hcp.eliquis.com

Please see Important Safety Information throughout and Full Prescribing Information, including Boxed WARNINGS, following page 15.
ELIQUIS® (apixaban) INDICATIONS

Approved for 6 indications

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF)
- for the treatment of deep vein thrombosis (DVT)
- for the treatment of pulmonary embolism (PE)
- to reduce the risk of recurrent DVT and PE following initial therapy
- for the prophylaxis of DVT, which may lead to PE, in patients who have undergone hip replacement surgery
- for the prophylaxis of DVT, which may lead to PE, in patients who have undergone knee replacement surgery

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS 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
- 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 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.

Please see Important Safety Information throughout and Full Prescribing Information, including Boxed WARNINGS, following page 15.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction in the risk of stroke/systemic embolism in NVAF</strong></td>
<td>5 mg twice daily in most patients</td>
</tr>
<tr>
<td><strong>Dose adjustment for NVAF patients:</strong></td>
<td>2.5 mg twice daily is recommended for patients with at least 2 of the following characteristics:</td>
</tr>
<tr>
<td>• age ≥80 years</td>
<td>• body weight ≤60 kg</td>
</tr>
<tr>
<td>• serum creatinine ≥1.5 mg/dL</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment of DVT/PE</strong></td>
<td>10 mg twice daily for the first 7 days</td>
</tr>
<tr>
<td>▼ After 7 days, transition to ▼</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td><strong>Reduction in the risk of recurrent DVT/PE following initial therapy</strong></td>
<td>2.5 mg twice daily after at least 6 months of treatment for DVT or PE</td>
</tr>
<tr>
<td><strong>Prophylaxis of DVT, which may lead to PE, following hip or knee replacement surgery</strong></td>
<td>2.5 mg twice daily for 35 days starting 12 to 24 hours after hip replacement surgery</td>
</tr>
<tr>
<td></td>
<td>2.5 mg twice daily for 12 days starting 12 to 24 hours after knee replacement surgery</td>
</tr>
</tbody>
</table>

**SELECTED IMPORTANT SAFETY INFORMATION**

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

Please see Important Safety Information throughout and Full Prescribing Information, including Boxed WARNINGS, following page 15.
For patients with NVAF, DOISING 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**

Patients with at least 2 of the following:

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

OR

For patients taking drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin).

**Note:** In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.

PLEASE SEE PAGES 8-14 FOR ADDITIONAL IMPORTANT DOSING INFORMATION.

SELECTED IMPORTANT SAFETY INFORMATION

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.

Please see Important Safety Information throughout and Full Prescribing Information, including Boxed WARNINGS, following page 15.
For patients with DVT/PE,

DOSING 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

<table>
<thead>
<tr>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg (two 5 mg tablets) twice daily</td>
</tr>
<tr>
<td>5 mg twice daily</td>
</tr>
</tbody>
</table>

Day 1 to Day 7

Following Day 7

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

<table>
<thead>
<tr>
<th>FOR</th>
<th>ADDRESS</th>
</tr>
</thead>
</table>

\[ Rx \]

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 8-14 FOR ADDITIONAL IMPORTANT DOSING INFORMATION.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - 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.
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

**Note:** For patients receiving ELIQUIS® (apixaban) doses of 5 mg or 10 mg twice daily, reduce the dose by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin).

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

**SELECTED IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS** (continued)

- **Bleeding Risk** (continued)
  - 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.
  - There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.
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

<table>
<thead>
<tr>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg twice daily</td>
</tr>
</tbody>
</table>

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
- **Recommended treatment duration for patients undergoing knee replacement surgery**: 12 DAYS

**Note:** In patients already taking 2.5 mg twice daily, coadministration of ELIQUIS® (apixaban) with strong dual inhibitors of CYP3A4 and P-gp should be avoided.

**PLEASE SEE PAGES 8-14 FOR ADDITIONAL IMPORTANT DOSING INFORMATION.**

**SELECTED IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (continued)**

- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS 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.
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

No dose adjustment required for patients with renal impairment 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

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

- Prosthetic Heart Valves: The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.

Please see Important Safety Information throughout and Full Prescribing Information, including Boxed WARNINGS, following page 15.
### Dosing in 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>
<tr>
<td>End-stage renal disease (ESRD)*</td>
<td>✓</td>
</tr>
</tbody>
</table>

No dose adjustment is recommended for patients with renal impairment alone, including those with end-stage renal disease (ESRD) maintained on hemodialysis, except for NVAF patients who meet the criteria for dosage adjustment.

*Patients with ESRD (CrCl < 15 mL/min) receiving or not receiving hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS® (apixaban); therefore, the dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis.

### SELECTED IMPORTANT SAFETY INFORMATION

**WARNINGS AND PRECAUTIONS (continued)**

- 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.
### Dosing in patients with hepatic impairment

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>hepatic impairment (Child-Pugh class A)</td>
<td>hepatic impairment (Child-Pugh class B)</td>
<td>hepatic impairment (Child-Pugh class C)</td>
</tr>
<tr>
<td>No dose adjustment required</td>
<td>There is limited clinical experience with ELIQUIS® (apixaban) in patients with moderate hepatic impairment; dosing recommendation cannot be provided</td>
<td>ELIQUIS is not recommended</td>
</tr>
</tbody>
</table>

### SELECTED IMPORTANT SAFETY INFORMATION

**ADVERSE REACTIONS**

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

Temporary interruption for surgery and other interventions

Elective surgery or invasive procedures with moderate or high risk of unacceptable or clinically significant bleeding

- Discontinue ELIQUIS at least 48 hours prior

Elective surgery or invasive procedures with low risk of bleeding or bleeding in noncritical site and easily controlled

- Discontinue ELIQUIS at least 24 hours prior

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.

SELECTED IMPORTANT SAFETY INFORMATION

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be 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.

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

Switching from warfarin to ELIQUIS

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

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

- 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.
- ELIQUIS affects INR, so that initial INR measurements during transition to warfarin may not be useful for determining the appropriate dose of warfarin.

Administration options

- For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS tablets may be crushed and suspended in 60 mL D5W and immediately delivered through a nasogastric tube. Information regarding the administration of crushed and suspended ELIQUIS tablets swallowed by mouth is not available

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

- Strong Dual Inhibitors of CYP3A4 and P-gp: Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) 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 strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.
DRUG INTERACTIONS

Strong dual inhibitors of CYP3A4 and P-gp

For patients receiving ELIQUIS® (apixaban) doses of 5 mg or 10 mg twice daily, reduce the dose by 50% if coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, such as:

- Ketoconazole
- Itraconazole
- Ritonavir
- Clarithromycin

In patients already taking ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp.

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

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS (continued)

- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

- **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.

Please see Important Safety Information throughout and Full Prescribing Information, including Boxed WARNINGS, following page 15.
**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.

**Additional considerations**

- 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. Adjust ELIQUIS dose for patients taking drugs that are strong dual inhibitors of 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.

**SELECTED IMPORTANT SAFETY INFORMATION**

**PREGNANCY CATEGORY B**

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

Please see Important Safety Information throughout and Full Prescribing Information, including Boxed WARNINGS, following page 15.
Approved for 6 Indications

Find out more at: hcp.eliquis.com

Reference: ELIQUIS® (apixaban) Package Insert.

Please see Important Safety Information throughout and Full Prescribing Information, including Boxed WARNINGS, following page 15.
ELIQUIS is a factor Xa inhibitor indicated:

- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT
- 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.
- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Dosage and Administration

- 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)

Dosage Forms and Strengths

- Tablets: 2.5 mg and 5 mg (3)

Contraindications

- Severe hypersensitivity to ELIQUIS (apixaban) (4)

Warnings and Precautions

- ELIQUIS can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of bleeding. (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 recurrence of DVT and PE following initial therapy:
- The recommended dose is 2.5 mg taken orally twice daily. (2.1)

Adverse Reactions

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

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

Drug Interactions

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

Use in Specific Populations

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2015
ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

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 ≥80 years
- body weight ≤60 kg
- serum creatinine ≥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.

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

2.4 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 parenteral anticoagulant and warfarin at the time the next dose of ELIQUIS would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

Switching 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 Strong Dual Inhibitors of CYP3A4 and P-glycoprotein

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 strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) [see Clinical Pharmacology (12.3)].

In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp [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 60 mL DSW and immediately delivered through a nasogastric tube (NGT) [see Clinical Pharmacology (12.3)]. Information regarding the administration of crushed and suspended ELIQUIS tablets swallowed by mouth is not available.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

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.

Reduction in the Risk of Recurrence of DVT and PE

The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE [see Clinical Studies (14.3)].
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 nonselective 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.

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure [see Clinical Pharmacology (12.3)]. Prothrombin complex concentrate or activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration [see Overdosage (10)].

6 ADVERSE REACTIONS

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

- Increased risk of thrombotic events after premature discontinuation [see Warnings and Precautions (5.1)]
- Bleeding [see Warnings and Precautions (5.2)]
- Spinal/epidural anesthesia or puncture [see Warnings and Precautions (5.3)]
Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

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>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>Major</td>
<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>
</tr>
<tr>
<td></td>
<td>First dose 12 to 24 hours post surgery</td>
<td>First dose 9 to 15 hours prior to surgery</td>
<td>First dose 12 to 24 hours post surgery</td>
</tr>
<tr>
<td></td>
<td>N = 2673</td>
<td>N = 2659</td>
<td>N = 1501</td>
</tr>
<tr>
<td>Major (including surgical site)</td>
<td>22 (0.82%)</td>
<td>18 (0.68%)</td>
<td>9 (0.6%)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hgb decrease ≥2 g/dL</td>
<td>13 (0.49%)</td>
<td>10 (0.38%)</td>
<td>8 (0.53%)</td>
</tr>
<tr>
<td>Transfusion of ≥2 units RBC</td>
<td>16 (0.60%)</td>
<td>14 (0.53%)</td>
<td>5 (0.33%)</td>
</tr>
</tbody>
</table>

Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into 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.
Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

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

**AMPLIFY Study**

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

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

Bleeding results from the AMPLIFY study are summarized in Table 5.

**Table 5:** Bleeding Results in the AMPLIFY Study

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

*CRNM = clinically relevant nonmajor bleeding.

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

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

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

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

**AMPLIFY-EXT Study**

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

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

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

7.3 Anticoagulants and Antiplatelet Agents
Co-administration of anticoagulant agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

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

8 USE IN SPECIFIC POPULATIONS

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

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to apixaban bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure based on unbound apixaban. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery.

There are no adequate and well-controlled studies of ELIQUIS in pregnant women.

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

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

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

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

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

8.5 Geriatric Use
Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 and older, and >31% were 75 and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 and older, while 16% were 75 and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 and older and >13% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

8.6 Renal Impairment
No dose adjustment is recommended for patients with renal impairment alone, including those with end-stage renal disease (ESRD) maintained on hemodialysis, except nonvalvular atrial fibrillation patients who meet the criteria for dosage adjustment [see Dosage and Administration (2.1)].

Patients with ESRD (CrCl <15 mL/min) receiving or not receiving hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the

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Table 7: Bleeding Results in the AMPLIFY-EXT Study

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS 2.5 mg bid</th>
<th>ELIQUIS 5 mg bid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=840</td>
<td>N=811</td>
<td>N=826</td>
</tr>
<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.

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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</th>
<th>ELIQUIS 5 mg bid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=840</td>
<td>N=811</td>
<td>N=826</td>
</tr>
<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>Contusion</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, periportal hematoma
Musculoskeletal and connective tissue disorders: muscle hemorrhage
Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, 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 Strong Dual Inhibitors of CYP3A4 and P-gp
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 strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) [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 strong dual inhibitors of CYP3A4 and P-gp [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)].
Apixaban is a white to pale-yellow powder. At physiological pH (1.2–6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL.

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

12 CLINICAL PHARMACOLOGY

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

12.2 Pharmacodynamics
As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban.

The Rotachrom® Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program.
Hemodialysis in ESRD subjects: Following a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min started 2 hours after administration of a single 5 mg dose of apixaban, the AUC of apixaban was 17% greater compared to those with normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min resulting in a 14% decrease in exposure due to hemodialysis compared to off-dialysis period.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Apixaban administered to female rats at doses up to 1000 mg/kg/day from implantation through the end of lactation produced no adverse findings in male offspring (F1 generation) at doses up to 1000 mg/kg/day, a dose resulting in exposure that is 5 times the human exposure. Adverse effects in the F1-generation female offspring were limited to decreased mating and fertility indices at 1000 mg/kg/day.

14 CLINICAL STUDIES

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

ARISTOTLE

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

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

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

A total of 18,201 patients were randomized and followed on study treatment for a median of 69 weeks. Forty-three percent of patients were vitamin K antagonist (VKA) “naive,” defined as having received <30 consecutive days of treatment with warfarin or another VKA before entering the study. The mean age was 69 years and the mean CHADS2 score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk) was 2.1. The population was 65% male, 83% Caucasian, 14% Asian, and 1% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 19% of patients. Concomitant diseases of patients in this study included hypertension 88%, diabetes 25%, congestive heart failure (or left ventricular ejection fraction ≤40%) 35%, and prior myocardial infarction 14%. Patients treated with warfarin in ARISTOTLE had a mean percentage of time in therapeutic range (INR 2.0–3.0) of 62%.
ELIQUIS® (apixaban) was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (Table 9 and Figure 4). Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs.

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

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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%/year)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>ELIQUIS 212 / 9120 (1.27)</td>
<td>Warfarin 265 / 9081 (1.60)</td>
<td>0.79 (0.66, 0.95)</td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>199 (1.19)</td>
<td>Warfarin 250 (1.51)</td>
<td>0.79 (0.65, 0.95)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without hemorrhage</td>
<td>140 (0.83)</td>
<td>136 (0.82)</td>
<td>1.02 (0.81, 1.29)</td>
</tr>
<tr>
<td>Ischemic with hemorrhagic conversion</td>
<td>12 (0.07)</td>
<td>20 (0.12)</td>
<td>0.60 (0.29, 1.23)</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, 1.29)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>15 (0.09)</td>
<td>17 (0.10)</td>
<td>0.87 (0.44, 1.75)</td>
</tr>
</tbody>
</table>

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

In ARISTOTLE, the results for the primary efficacy endpoint were generally consistent across most major subgroups including weight, CHADS2 score (a scale from 0 to 6 used to predict risk of stroke in patients with AF, with higher scores predicting greater risk), prior warfarin use, level of renal impairment, geographic region, and aspirin use at randomization (Figure 5).

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

Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into 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)].

AVERROES

In AVERROES, patients with nonvalvular atrial fibrillation thought not to be candidates for warfarin therapy were randomized to treatment with ELIQUIS 5 mg orally twice daily (or 2.5 mg twice daily in selected patients) or aspirin 81 to 324 mg once daily. The primary objective of the study was to determine if ELIQUIS was superior to aspirin for preventing the composite outcome of stroke or systemic embolism. AVERROES was stopped early on the basis of a prespecified interim analysis showing a significant reduction in stroke and systemic embolism for ELIQUIS compared to aspirin that was associated with a modest increase in major bleeding (Table 10) [see Adverse Reactions (6.1)].

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

<table>
<thead>
<tr>
<th>ELIQUIS</th>
<th>Aspirin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td></td>
<td>0.45 (0.32, 0.62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>0.44 (0.31, 0.63)</td>
<td>-</td>
</tr>
<tr>
<td>Ischemic or undetermined</td>
<td></td>
<td>0.67 (0.24, 1.88)</td>
<td>-</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td>0.15 (0.03, 0.68)</td>
<td>-</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td></td>
<td>0.79 (0.62, 1.02)</td>
<td>0.068</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td>0.57 (0.45, 0.71)</td>
<td>-</td>
</tr>
<tr>
<td>All-cause death</td>
<td></td>
<td>0.67 (0.65, 1.17)</td>
<td>-</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>ELIQUIS</th>
<th>Enoxaparin</th>
<th>Relative Risk (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERG-3</td>
<td>2.5 mg po bid</td>
<td>104 (8.99%)</td>
<td>91 (8.03%)</td>
</tr>
<tr>
<td>Enoxaparin 40 mg sc qd</td>
<td>100 (8.85%)</td>
<td>115 (9.82%)</td>
<td>0.86 (0.64, 1.15)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>ELIQUIS</th>
<th>Enoxaparin 30 mg sc q12h</th>
<th>Relative Risk (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE-1</td>
<td>2.5 mg po bid</td>
<td>104 (8.99%)</td>
<td>91 (8.03%)</td>
</tr>
<tr>
<td>Enoxaparin 40 mg sc qd</td>
<td>100 (8.85%)</td>
<td>115 (9.82%)</td>
<td>0.86 (0.64, 1.15)</td>
</tr>
</tbody>
</table>

The efficacy profile of ELIQUIS was generally consistent across subgroups of interest for this indication (e.g., age, gender, race, body weight, renal impairment).
14.3 Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

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

AMPLIFY

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

Table 13: Efficacy Results in the AMPLIFY Study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ELIQUIS 2.5 mg bid N=840</th>
<th>Enoxaparin/Warfarin N=835</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE or VTE-related death*</td>
<td>59 (2.3%)</td>
<td>71 (2.7%)</td>
<td>0.84 (0.60, 1.18)</td>
</tr>
<tr>
<td>DVT†</td>
<td>22 (0.8%)</td>
<td>35 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>PE†</td>
<td>27 (1.0%)</td>
<td>25 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>VTE-related death†</td>
<td>12 (0.4%)</td>
<td>16 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>VTE or all-cause death</td>
<td>84 (3.2%)</td>
<td>104 (4.0%)</td>
<td>0.82 (0.61, 1.08)</td>
</tr>
<tr>
<td>VTE or CV-related death</td>
<td>61 (2.3%)</td>
<td>77 (2.9%)</td>
<td>0.80 (0.57, 1.11)</td>
</tr>
</tbody>
</table>

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

In the AMPLIFY study, patients were stratified according to their index event of PE (with or without DVT) or DVT (without PE). Efficacy in the initial treatment of VTE was noninferior to enoxaparin/warfarin (P-value <0.0001).

PE* 23 (2.7) 25 (3.1) 37 (4.5)
All-cause death 22 (2.6) 25 (3.1) 33 (4.0)

Table 14: Efficacy Results in the AMPLIFY-EXT Study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ELIQUIS 2.5 mg bid N=813</th>
<th>ELIQUIS 5 mg bid N=829</th>
<th>Placebo N=829</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE or all-cause death</td>
<td>32 (3.8)</td>
<td>34 (4.2)</td>
<td>96 (11.6)</td>
<td>0.33 (0.22, 0.48) 0.36 (0.25, 0.53)</td>
</tr>
<tr>
<td>DVT*</td>
<td>19 (2.3)</td>
<td>28 (3.4)</td>
<td>72 (8.7)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>PE*</td>
<td>23 (2.7)</td>
<td>25 (3.1)</td>
<td>37 (4.5)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>All-cause death</td>
<td>22 (2.6)</td>
<td>25 (3.1)</td>
<td>33 (4.0)</td>
<td></td>
</tr>
</tbody>
</table>

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

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

Table 15: ELIQUIS Tablets

<table>
<thead>
<tr>
<th>Strength</th>
<th>Tablet Color/Shape</th>
<th>Tablet Markings</th>
<th>Package Size</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
<td>Yellow, round</td>
<td>“893” on one side and “2½” on the other side</td>
<td>Bottles of 60</td>
<td>0003-0893-21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bottles of 180 Hospital Unit-Dose Blister Package of 100</td>
<td>0003-0893-41</td>
</tr>
<tr>
<td>5 mg</td>
<td>Pink, oval</td>
<td>“894” on one side and “5” on the other side</td>
<td>Bottles of 60</td>
<td>0003-0894-21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bottles of 180 Hospital Unit-Dose Blister Package of 100</td>
<td>0003-0894-41</td>
</tr>
</tbody>
</table>

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

• They should not discontinue ELIQUIS without talking to their physician first.

• They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.

• They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.

• If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel or bladder dysfunction [see Warnings and Precautions (5.3)]. If any of these symptoms occur, the patient should contact his or her physician immediately.

• They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding and may be breastfeeding during treatment with ELIQUIS [see Use in Specific Populations (8.1, 8.3)].

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

Marketed by:

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

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1356615A0 / 1356514A0
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)

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

While taking ELIQUIS:

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

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

• unexpected bleeding, or bleeding that lasts a long time, such as:
  • unusual bleeding from the gums
  • nosebleeds that happen often
  • menstrual bleeding or vaginal bleeding that is heavier than normal

  • bleeding that is severe or you cannot control
  • red, pink, or brown urine
  • red or black stools (looks like tar)
  • cough up blood or blood clots
  • vomit blood or your vomit looks like coffee grounds
  • unexpected pain, swelling, or joint pain
  • headaches, feeling dizzy or weak

• ELIQUIS is not for patients with artificial heart valves.

• Spinal or epidural blood clots (hematoma). People who take a blood thinner medicine (anticoagulant) like ELIQUIS, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  • a thin tube called an epidural catheter is placed in your back to give you certain medicine
• you take NSAIDs or a medicine to prevent blood from clotting
• you have a history of difficult or repeated epidural or spinal punctures
• you have a history of problems with your spine or have had surgery on your spine

If you take ELIQUIS and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots or bleeding. Tell your doctor right away if you have tingling, numbness, or muscle weakness, especially in your legs and feet.

What is ELIQUIS?
ELIQUIS is a prescription medicine used to:
• reduce the risk of stroke and blood clots in people who have atrial fibrillation.
• reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.
• treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism), and reduce the risk of them occurring again.

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

Who should not take ELIQUIS?
Do not take ELIQUIS if you:
• currently have certain types of abnormal bleeding.
• have had a serious allergic reaction to ELIQUIS. Ask your doctor if you are not sure.

What should I tell my doctor before taking ELIQUIS?
Before you take ELIQUIS, tell your doctor if you:
• have kidney or liver problems
• have any other medical condition
• have ever had bleeding problems
• are pregnant or plan to become pregnant. It is not known if ELIQUIS will harm your unborn baby.

• are breastfeeding or plan to breastfeed. It is not known if ELIQUIS passes into your breast milk. You and your doctor should decide if you will take ELIQUIS or breastfeed. You should not do both.

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

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

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

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

What are the possible side effects of ELIQUIS?

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

ELIQUIS can cause a skin rash or severe allergic reaction. Call your doctor or get medical help right away if you have any of the following symptoms:

• chest pain or tightness
• swelling of your face or tongue
• trouble breathing or wheezing
• feeling dizzy or faint

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

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

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

How should I store ELIQUIS?

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

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

General Information about ELIQUIS

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

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

For more information, call 1-855-354-7847 (1-855-ELIQUIS) or go to www.ELIQUIS.com.

What are the ingredients in ELIQUIS?

Active ingredient: apixaban.

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

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

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and
Pfizer Inc
New York, New York 10017 USA

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