COME TAKE PART IN AN EXPERT THEATER

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and reduction in the risk of recurrent DVT and PE following initial therapy.

PRESENTED BY

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Date: 8/29/19
Time: 11:30 AM–12:30 PM
Location:
NORTHWESTERN MEMORIAL HOSPITAL
251 E. HURON ST
CHICAGO, IL 60611

INDICATIONS

ELIQUIS 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.

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.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (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.

Please see Full Prescribing Information, including Boxed WARNINGS, attached.
WARNINGS AND PRECAUTIONS (cont’d)

• **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.
  – 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.
  – 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 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 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.

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 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 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 antithrombotic 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 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.
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. Patients with Antiphospholipid Syndromes

Direct oral anticoagulants (DOACs) including ELIQUIS are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome (APS). In particular, antiphospholipid syndrome patients who are positive for lupus anticoagulant, anti-beta-2-glycoprotein I antibodies, treatment with DOACs should be associated with increased rates of recurrent thrombosis compared to vitamin K antagonist therapy. The efficacy and safety of ELIQUIS in patients with APS have not been established.

ADVERSE REACTIONS

The following 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]
• Bleeding [see Warnings and Precautions]
• Clinical Trials or population [see Warnings and Precautions]

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

Reduction of Risk in Occurrence of DVT and PE—ELIQUIS is indicated to reduce the risk of recurrent stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

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.

Treatment of Deep Vein Thrombosis—ELIQUIS is indicated for the treatment of DVT. Treatment of Pulmonary Embolism—ELIQUIS is indicated for the treatment of PE.

DOSAGE AND ADMINISTRATION (Selected 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 uncontrolled or clinically significant bleeding [see Warnings and Precautions]. If surgery or invasive procedures are performed within a few days after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted based on the planned time of the next procedure(s) and the risk of the procedure. (For complete Dose and Administration section, see full Prescribing Information.)

CONTINUATIONS

ELIQUIS is contraindicated in patients with the following conditions:

• Active peptic ulcer disease [see Warnings and Precautions and Adverse Reactions]
• Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) [see Adverse Reactions]

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, is associated with an increased risk of thrombotic events. An increased rate of stroke was observed during the treatment with ELIQUIS in a clinical trial in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or another drug and may not reflect the rates observed in practice.

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including a total of 738 patients exposed to ELIQUIS.25 mg twice daily undergoing major hip or knee surgery of the lower limbs (elective hip replacement or elective knee replacement) treated up to 36 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. ELIQUIS was assessed in each study 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

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<td>3 (0.9%)</td>
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* All bleeding criteria included clinical, hematologically confirmed, or both
† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban
§ Includes the patients undergoing reoperation or reintervention, intramuscular, intravenous, or intraluminal intervention, or noninterventional intervention.

100 pt-year

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CRNM = clinically relevant non-major 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 7.

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

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Risk Summary

There are no data on the presence of apixaban or its metabolites in human milk, the effects of the drug on milk, or the effects on infant growth and development. Breastfeeding is not recommended during treatment with ELIQUIS (apixaban).

Additional Data

Maternal 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 hours) ratio was 0.8 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.

Lactation

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the AMPLIFY and AMPLIFY-EXT clinical studies, 66% were 65 years of age or older, and 31% were 75 years of age or older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 56% of subjects were 65 years of age or older. Of the 15% of subjects enrolled in each of the studies, 16% were 65 years of age and older and 3% were 75 years of age and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

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) in Full Prescribing Information):

- age ≥ 65 years
- body weight less than or equal to 60 kg
- severe renal impairment 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 on dialysis or with ESRD (n=15 subjects) because such patients were expected to have a high risk of bleeding and the risk of thromboembolism in this population was not assessed. Clinical information about the use of ELIQUIS in patients with ESRD on dialysis was not seen in AMPLIFY or AMPLIFY-EXT.

OVERDOSAGE

Overdose of ELIQUIS increases the risk of bleeding (seeWARNINGS and PRECAUTIONS).

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 70 mg daily for 3 days or 60 mg once daily for 3 days had no clinically relevant adverse effects.

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

PREGNANCY COUNSELING INFORMATION

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

Advise patients of the following:

- to NOT discontinue ELIQUIS without talking to their physician first.
- that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS.
- to tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any injured limb is taken.
- that they are at an increased risk of bleeding due to the presence of the product in the human body. ELIQUIS has also been shown to increase the risk of bleeding and the risk of hemorrhage.
- to tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding.
- that they should use non-prescription drugs, such as aspirin or NSAIDs, only under medical supervision.
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