Getting Started on ELIQUIS to reduce your risk of stroke due to atrial fibrillation (AFib), a type of irregular heartbeat, not caused by a heart valve problem

SEE INSIDE FOR INFORMATION ON:

- How to take ELIQUIS
- ELIQUIS savings and support, including Co-pay Card
- AFib not caused by a heart valve problem

Selected Important Safety Information

For people taking ELIQUIS® (apixaban) for atrial fibrillation: Do not stop taking ELIQUIS without talking to the doctor who prescribed it for you. Stopping ELIQUIS increases your risk of having a stroke.

ELIQUIS can cause bleeding, which can be serious, and rarely may lead to death.

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.

Joseph is a real ELIQUIS patient. He was compensated for his time and expenses.
Welcome!

Selected Important Safety Information
ELIQUIS may need to be stopped prior to surgery or a medical or dental procedure. Your doctor will tell you when you should stop taking ELIQUIS and when you may start taking it again. If you have to stop taking ELIQUIS, your doctor may prescribe another medicine to help prevent a blood clot from forming.

Why May My Doctor Have Prescribed ELIQUIS® (apixaban)?
Explore how ELIQUIS may help with your condition

How Do I Take ELIQUIS?
Review some do's and don'ts before starting ELIQUIS

How Can I Get Savings & Support?
Learn about savings offers and sign up for support

What Should I Know About AFib?
Learn about AFib not caused by a heart valve problem and its risk of stroke
Go to www.moblguide.com on your phone to get information about starting ELIQUIS® (apixaban).

Watch our Simple Science Video Series, brought to you by Dr. Why.

Dr. Why is a fictional character.

Selected Important Safety Information

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.

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.

Why May My Doctor Have Prescribed ELIQUIS?

EXPLORE THIS SECTION TO LEARN ABOUT:

- How ELIQUIS works
- How ELIQUIS performed in clinical trials
- Other reasons to consider ELIQUIS
- Tips for talking with your doctor
“MY CARDIOLOGIST AND I DECIDED TOGETHER THAT ELIQUIS WAS THE WAY TO GO FOR ME.”
—Fred, a real ELIQUIS patient

Watch Fred tell his story at www.ELIQUIS.com/fred

We asked patients to tell us about their experience with ELIQUIS. Fred was compensated for his time and expenses.

What Is ELIQUIS?

If you’ve been diagnosed with atrial fibrillation (AFib), a type of irregular heartbeat, not caused by a heart valve problem, your doctor may have prescribed ELIQUIS.

ELIQUIS is a prescription blood thinner medication that lowers the chance of blood clots forming in your body.

ELIQUIS works by blocking Factor Xa, which is a blood clotting factor critical to the blood clotting process. By blocking Factor Xa, ELIQUIS lowers the chance of blood clots forming and decreases the risk of having a stroke in people with AFib.

Selected Important Safety Information

You may have a higher risk of bleeding if you take ELIQUIS and take other medicines that increase your risk of bleeding, such as aspirin, nonsteroidal anti-inflammatory drugs (called NSAIDs), warfarin (COUMADIN®), heparin, selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and other medicines to help prevent or treat blood clots. Tell your doctor about all of the medicines you take, including any over-the-counter medicines, vitamins, and herbal supplements.

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
WHY ELIQUIS

ELIQUIS Is Supported by Extensive Clinical Research

ELIQUIS was studied in 2 clinical trials to evaluate reducing the risk of stroke and blood clots in people with atrial fibrillation (AFib), a type of irregular heartbeat, not caused by a heart valve problem:

\[\text{~24,000} \quad \text{PEOPLE PARTICIPATED IN 2 STUDIES} \]

\[\text{>11,000} \quad \text{OF THE PEOPLE STUDIED TOOK ELIQUIS} \]

**Trial One:** Compared ELIQUIS to warfarin in people with AFib not caused by a heart valve problem.

**Trial Two:** Compared ELIQUIS to aspirin in people with AFib not caused by a heart valve problem who were not suitable for treatment with warfarin.

Based on the results of these clinical trials, ELIQUIS was approved to reduce the risk of stroke and blood clots in people with AFib, a type of irregular heartbeat, not caused by a heart valve problem.

In Trial One, ELIQUIS had significantly less major bleeding than warfarin. In Trial Two, ELIQUIS had a modest increase in major bleeding compared to aspirin.

**ELIQUIS and other blood thinners increase the risk of bleeding, which can be serious, and rarely may lead to death.**

In Trial One, ELIQUIS Was Proven Better Than Warfarin

In people with AFib not caused by a heart valve problem, ELIQUIS:

**REDUCED THE RISK OF STROKE BETTER THAN WARFARIN**

**HAD SIGNIFICANTLY LESS MAJOR BLEEDING* THAN WARFARIN**

In Trial Two, ELIQUIS had a modest increase in major bleeding compared to aspirin.

ELIQUIS and other blood thinners increase the risk of bleeding, which can be serious, and rarely may lead to death.

*Major bleeding included noticeable bleeding with at least 1 of the following—a transfusion of 2 or more units of blood; bleeding that occurred in the brain, spine, eye, around the heart, in a joint, or in a muscle, leading to damage; or fatal bleeding.

Selected Important Safety Information

While taking ELIQUIS, you may bruise more easily and 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, or menstrual 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)

(Bleeding Symptoms Continued on Next Page)

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
WHY ELIQUIS

Other Reasons to Consider ELIQUIS

No Routine INR Blood Testing
With ELIQUIS, there is no routine INR (International Normalized Ratio) blood testing, also called INR monitoring. The INR test checks to see how fast your blood clots. Warfarin is a medication with a “narrow therapeutic range,” meaning that small changes in the medication level may have an impact on the time it takes for blood to clot. Because of this, people taking warfarin need to monitor their INR to keep their medication level in the target range. ELIQUIS does not have a narrow therapeutic range; therefore, if you’re taking ELIQUIS, you don’t need to have routine INR blood testing.

No Regular Dose Adjustment
Take ELIQUIS exactly as prescribed by your doctor. ELIQUIS comes in either a 5-mg or 2.5-mg tablet. Most people with atrial fibrillation (AFib) not caused by a heart valve problem will be prescribed 5 mg twice a day to reduce the risk of stroke. Be sure to tell your doctor about all medications you take and your medical history, as the lower dose may be appropriate for you. ELIQUIS doesn't require regular dose adjustments.

Selected Important Safety Information
(Bleeding Symptoms Continued)
- coughing up or vomiting blood or vomit that looks like coffee grounds
- unexpected pain, swelling, or joint pain
- headaches, or feeling dizzy or weak

ELIQUIS (apixaban) is not for patients with artificial heart valves.
Spinal or epidural blood clots (hematoma). People who take 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

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.

Eat the Healthy Foods You Enjoy
Unlike warfarin, there are no “watch-outs” for certain foods like green leafy vegetables when taking ELIQUIS. With ELIQUIS, you can continue eating the healthy foods you like. Also, ELIQUIS may be taken with or without food. It doesn’t have to be timed to a meal.
Questions? Ask Your Doctor

As you begin taking ELIQUIS® (apixaban), don't forget to make a follow-up appointment with your doctor to discuss any questions you may have about ELIQUIS.

Print our list of questions to ask your doctor and bring it to your next appointment. Download the questions at www.ELIQUIS.com/questions

Selected Important Safety Information
(Spinal or Epidural Blood Clot Risks Continued)

- 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

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
“MY DOCTOR TALKED TO ME ABOUT STARTING TREATMENT TO REDUCE MY RISK OF A STROKE.”

—Allie, a real ELIQUIS patient

We asked patients to tell us about their experience with ELIQUIS. Allie was compensated for her time and expenses.

Watch Allie tell her story at www.ELIQUIS.com/allie

How Do I Take ELIQUIS?

ELIQUIS is available in 2.5-mg and 5-mg tablets. Before you begin taking ELIQUIS, tell your doctor about all medications you take and your medical history, as the lower dose may be appropriate for you.

Selected Important Safety Information

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.

Do not take ELIQUIS if you currently have certain types of abnormal bleeding or have had a serious allergic reaction to ELIQUIS.

Before you take ELIQUIS, tell your doctor if you have kidney or liver problems, have any other medical condition, or have ever had bleeding problems. Tell your doctor if you are pregnant or breastfeeding, or plan to become pregnant or breastfeed. You and your doctor should decide if you will take ELIQUIS or breastfeed. You should not do both.

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
Some ELIQUIS Do’s and Don’ts

Be sure to take ELIQUIS exactly as prescribed by your doctor.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take ELIQUIS. 5-mg and 2.5-mg ELIQUIS tablets may be crushed and put into water or apple juice, or mixed with applesauce to be taken promptly within four hours. Talk to your doctor about the best way for you to take ELIQUIS.

Take ELIQUIS twice every day with or without food, and store at room temperature.

If you miss a dose of ELIQUIS, take it as soon as you remember, and do not take more than one dose at the same time to make up for a missed dose.

Don’t take ELIQUIS if you currently have certain types of abnormal bleeding, or if you’ve had a serious allergic reaction to ELIQUIS. Call your doctor or get medical help right away if you experience chest pain or tightness, swelling of your face or tongue, trouble breathing or wheezing, feelings of dizziness or faintness.

Do not change your dose or stop taking ELIQUIS unless your doctor tells you to. 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.

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.

Selected Important Safety Information

Take ELIQUIS exactly as prescribed by your doctor. Take ELIQUIS twice every day with or without food, and do not change your dose or stop taking it unless your doctor tells you to. If you miss a dose of ELIQUIS, take it as soon as you remember, and do not take more than one dose at the same time. 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.

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
Tips for Remembering to Take ELIQUIS® (apixaban)

If you’re having trouble remembering to take your medication, these simple suggestions may help:

Set alarms or alerts: Use your watch or, if you have one, your smartphone.

Make it a habit: Take your medication at the same time each morning and evening. You can even time it to a daily activity, like brushing your teeth.

Keep your meds in sight: Consider places like your kitchen counter or bedroom dresser (but always keep medications away from children).

Selected Important Safety Information

Possible serious side effects include bleeding or a reaction to ELIQUIS itself. A reaction to ELIQUIS can cause hives, rash, itching, and possibly trouble breathing. If you get this reaction, it will usually happen soon after you take a dose of ELIQUIS. Get medical help right away if you have sudden chest pain or chest tightness, have sudden swelling of your face or tongue, have trouble breathing, wheezing, or feeling dizzy or faint.

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
“THERE ARE MANY QUESTIONS THAT PEOPLE HAVE THAT THEY DON’T ASK.”

—Joseph, a real ELIQUIS patient

Watch Joseph tell his story
www.ELIQUIS.com/joseph

How Can I Get Savings & Support?

If you’re living with AFib not caused by a heart valve problem, it helps to have ongoing support. ELIQUIS 360 Support is here to help.

360 Support Emails and Newsletters Include:

- Interesting facts about AFib not caused by a heart valve problem
- Valuable tips and guidance for living with your condition
- Information about reducing the risk of stroke due to AFib not caused by a heart valve problem

We also have a team of live representatives that can help you understand insurance coverage. Flip to the next page to learn how to sign up for ELIQUIS 360 Support.

Selected Important Safety Information

For people taking ELIQUIS® (apixaban) for atrial fibrillation:
Do not stop taking ELIQUIS without talking to the doctor who prescribed it for you. Stopping ELIQUIS increases your risk of having a stroke.

ELIQUIS may need to be stopped prior to surgery or a medical or dental procedure. Your doctor will tell you when you should stop taking ELIQUIS and when you may start taking it again. If you have to stop taking ELIQUIS, your doctor may prescribe another medicine to help prevent a blood clot from forming.
Sign Up for ELIQUIS 360 Support

Need help with co-pays or determining your prescription coverage? Want to learn more about AFib not caused by a heart valve problem and ELIQUIS? ELIQUIS 360 Support is here to help. Sign up to receive newsletters and emails by:

- Visiting www.ELIQUIS.com/enroll
- Calling us at the number below

Call 1-855-ELIQUIS (354-7847)
Mon – Fri, 8 AM – 8 PM (EST) or
Sat – Sun, 9 AM – 6 PM (EST)

Selected Important Safety Information

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.

Save on ELIQUIS

Activate Your Co-pay Card

For ELIQUIS patients who qualify, we offer the Co-pay Card to help with out-of-pocket costs for ELIQUIS, and a Free Trial Offer Card. To see if you are eligible to take advantage of these offers visit www.ELIQUIS.com/request.

Help Understanding Your Insurance Coverage

Understanding insurance coverage can be complicated and time consuming. Let us help make it easier. Live representatives are here to:

- Help you find out if ELIQUIS is covered by your insurance plan
- Determine if you are eligible for assistance paying for ELIQUIS
- Check if you qualify for the ELIQUIS Co-pay Card

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
Representatives Can Also Help With:

Prior authorization: If your insurance plan needs prior authorization before approving coverage of ELIQUIS® (apixaban), representatives can help coordinate the process among your doctors, insurer, and pharmacist, and get the paperwork submitted.

Formulary exception requests: A formulary is an insurance company’s list of covered medications. Some insurance plans may not cover ELIQUIS, or will ask that a formulary exception request be submitted. Our live agents can provide general information to help you and your healthcare prescriber with the exception process. If your prescriber is unable to get ELIQUIS approved, and if you are eligible, we will refer you to our co-pay assistance program or the patient assistance program.

Selected Important Safety Information

You may have a higher risk of bleeding if you take ELIQUIS and take other medicines that increase your risk of bleeding, such as aspirin, nonsteroidal anti-inflammatory drugs (called NSAIDs), warfarin (COUMADIN®), heparin, selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and other medicines to help prevent or treat blood clots. Tell your doctor about all of the medicines you take, including any over-the-counter medicines, vitamins, and herbal supplements.

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
“I BELIEVE IT’S IMPORTANT TO HAVE A GOOD CONVERSATION WITH ALL OF MY PATIENTS.”

—Dr. Nayak, board-certified in Cardiovascular Disease and Clinical Cardiac Electrophysiology

What is AFib Not Caused by a Heart Valve Problem?

There are 2 types of AFib: one that is caused by a heart valve problem, and one that is not. Most cases of AFib are not caused by a heart valve problem. AFib not caused by a heart valve problem means the same thing as “nonvalvular atrial fibrillation,” or NVAF.

In 2014, it was estimated that about 6.4 million people in the U.S. had AFib not caused by a heart valve problem.

Selected Important Safety Information

While taking ELIQUIS, you may bruise more easily and 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, or menstrual 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)

(Bleeding Symptoms Continued on Next Page)
How Can AFib Lead to a Clot?

1. If you have AFib, the top 2 chambers of your heart, called the atria, quiver (fibrillate) instead of contracting with a full squeeze.
2. Because of this, the atria do not push all the blood out to where it should go, the ventricles.
3. The blood left in the atria can pool and clump together, increasing the risk for clots to form.

How Can a Clot Lead to a Stroke?

If a clot breaks loose and travels to the brain, blocking or limiting blood flow, it can cause a stroke, as shown in the graphic below:

Selected Important Safety Information

(Bleeding Symptoms Continued)

- coughing up or vomiting blood or vomit that looks like coffee grounds
- unexpected pain, swelling, or joint pain
- headaches, or feeling dizzy or weak

ELIQUIS (apixaban) is not for patients with artificial heart valves.

Watch Dr. Why show how AFib can lead to a stroke at www.ELIQUIS.com/stroke
Visit www.ELIQUIS.com to:

- Learn more about your condition and ELIQUIS
- Sign up for 360 Support

Or, visit moblguide.com for quick access to:

- Our Simple Science Video Series and more resources on your smartphone

Call 1-855-ELIQUIS (354-7847)
Mon – Fri, 8 AM – 8 PM (EST) or
Sat – Sun, 9 AM – 6 PM (EST)

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

Initial U.S. Approval: 2012

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

See full prescribing information for complete boxed warning.

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy. (2.4, 5.1, 14.1)

(B) SPINAL/EPIDURAL HEMATOMA: 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. (5.3)

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INDICATIONS AND USAGE

ELIQUIS is a factor Xa inhibitor indicated:
- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: (1.1)
- for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery. (1.2)
- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. (1.3, 1.4, 1.5)

DOSE AND ADMINISTRATION

- Reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation:
  - The recommended dose is 5 mg orally twice daily. (2.1)
  - In patients with at least 2 of the following characteristics: age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. (2.1)

FULL PRESCRIBING INFORMATION: CONTENTS

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

1 INDICATIONS AND USAGE

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

1.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

1.3 Treatment of Deep Vein Thrombosis

1.4 Treatment of Pulmonary Embolism

1.5 Reduction in the Risk of Recurrence of DVT and PE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

2.2 Missed Dose

2.3 Temporary Interruption for Surgery and Other Interventions

2.4 Converting from or to ELIQUIS

2.5 Combined P-gp and Strong CYP3A4 Inhibitors

2.6 Administration Options

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

5.2 Bleeding

5.3 Spinal/Epidural Anesthesia or Puncture

5.4 Patients with Prosthetic Heart Valves

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban. Reduce ELIQUIS dose or avoid coadministration. (2.5, 7.1, 12.3)

8 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: 2/2018

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**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.

**DOSES 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.

**WARNINGS AND PRECAUTIONS**

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

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 [see Dosage and Administration (2.4), Warnings and Precautions (5.1), 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)].

5.3 Increased Risk of Thrombotic Events after Premature Discontinuation

5.4 Increased Risk of Intracranial Hemorrhage

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)]

5.5 Risks of Combined Oral Anticoagulants

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding [see Dosage and Administration (2.1) and Adverse Reactions (6.1)].
Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) [see Drug Interactions (7.3)].

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

Reversal of Anticoagulant Effect

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

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 and aprotinin) in individuals receiving apixaban, and they are not expected to be effective as a reversal agent.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, 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 Thrombolytic or Pulmonary Embolectomy

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies [see Clinical Studies (14)], including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

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

<table>
<thead>
<tr>
<th>Major†</th>
<th>ELIQUIS</th>
<th>Warfarin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial (ICH)‡</td>
<td>327 (2.13)</td>
<td>462 (3.09)</td>
<td>0.69 (0.60, 0.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemorrhagic stroke§</td>
<td>52 (0.33)</td>
<td>125 (0.82)</td>
<td>0.41 (0.30, 0.57)</td>
<td>-</td>
</tr>
<tr>
<td>Other ICH</td>
<td>38 (0.24)</td>
<td>74 (0.49)</td>
<td>0.51 (0.34, 0.75)</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal (GI)¶</td>
<td>15 (0.10)</td>
<td>51 (0.34)</td>
<td>0.29 (0.16, 0.51)</td>
<td>-</td>
</tr>
<tr>
<td>Fatal**</td>
<td>128 (0.83)</td>
<td>141 (0.93)</td>
<td>0.89 (0.70, 1.14)</td>
<td>-</td>
</tr>
<tr>
<td>Intracranial</td>
<td>10 (0.06)</td>
<td>37 (0.24)</td>
<td>0.27 (0.13, 0.53)</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal (GI)¶</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).
† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, retroperitoneal or with fatal outcome.
‡ Intracranial bleeding includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an 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.
** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, CHA2DS2 score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).
ELIQUIS® (apixaban)

**Figure 1: Major Bleeding 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>232 / 9088 (2.1)</td>
<td>462 / 9052 (3.1)</td>
<td>0.69 (0.60, 0.80)</td>
</tr>
<tr>
<td>Prior Warfarin/VKA Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experienced (57%)</td>
<td>185 / 5196 (2.1)</td>
<td>274 / 5180 (3.2)</td>
<td>0.66 (0.55, 0.80)</td>
</tr>
<tr>
<td>Naive (43%)</td>
<td>142 / 3892 (2.2)</td>
<td>188 / 3872 (3.0)</td>
<td>0.73 (0.59, 0.91)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 (30%)</td>
<td>56 / 2723 (1.2)</td>
<td>72 / 2732 (1.5)</td>
<td>0.78 (0.55, 1.11)</td>
</tr>
<tr>
<td>≥65 and &lt;75 (39%)</td>
<td>120 / 3529 (2.0)</td>
<td>166 / 3501 (2.8)</td>
<td>0.71 (0.56, 0.89)</td>
</tr>
<tr>
<td>≥75 (31%)</td>
<td>151 / 2836 (3.3)</td>
<td>224 / 2819 (5.2)</td>
<td>0.64 (0.52, 0.79)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (65%)</td>
<td>225 / 5868 (2.3)</td>
<td>294 / 5879 (3.0)</td>
<td>0.76 (0.64, 0.90)</td>
</tr>
<tr>
<td>Female (35%)</td>
<td>102 / 3220 (1.9)</td>
<td>168 / 3173 (3.3)</td>
<td>0.58 (0.45, 0.74)</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 kg (11%)</td>
<td>36 / 1013 (2.3)</td>
<td>62 / 965 (4.3)</td>
<td>0.55 (0.36, 0.83)</td>
</tr>
<tr>
<td>&gt;60 kg (89%)</td>
<td>290 / 8043 (2.1)</td>
<td>398 / 8059 (3.0)</td>
<td>0.72 (0.62, 0.83)</td>
</tr>
<tr>
<td>Prior Stroke or TIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (19%)</td>
<td>77 / 1687 (2.8)</td>
<td>106 / 1735 (3.9)</td>
<td>0.73 (0.54, 0.98)</td>
</tr>
<tr>
<td>No (81%)</td>
<td>250 / 7401 (2.0)</td>
<td>356 / 7317 (2.9)</td>
<td>0.68 (0.58, 0.80)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (25%)</td>
<td>112 / 2276 (3.0)</td>
<td>114 / 2250 (3.1)</td>
<td>0.96 (0.74, 1.25)</td>
</tr>
<tr>
<td>No (75%)</td>
<td>215 / 6812 (1.9)</td>
<td>348 / 6808 (3.1)</td>
<td>0.60 (0.51, 0.71)</td>
</tr>
<tr>
<td>CHADS2 Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 (34%)</td>
<td>76 / 3093 (1.4)</td>
<td>126 / 3076 (2.3)</td>
<td>0.59 (0.44, 0.78)</td>
</tr>
<tr>
<td>2 (36%)</td>
<td>125 / 3246 (2.3)</td>
<td>163 / 3246 (3.0)</td>
<td>0.76 (0.60, 0.96)</td>
</tr>
<tr>
<td>≥3 (30%)</td>
<td>126 / 2749 (2.9)</td>
<td>173 / 2730 (4.1)</td>
<td>0.70 (0.56, 0.88)</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 mL/min (1%)</td>
<td>7 / 136 (3.7)</td>
<td>19 / 132 (11.9)</td>
<td>0.32 (0.13, 0.78)</td>
</tr>
<tr>
<td>30-50 mL/min (15%)</td>
<td>66 / 1357 (3.2)</td>
<td>123 / 1380 (6.0)</td>
<td>0.53 (0.39, 0.71)</td>
</tr>
<tr>
<td>&gt;50-80 mL/min (42%)</td>
<td>157 / 3807 (2.5)</td>
<td>199 / 3758 (3.2)</td>
<td>0.76 (0.62, 0.94)</td>
</tr>
<tr>
<td>&gt;80 mL/min (41%)</td>
<td>96 / 3750 (1.5)</td>
<td>119 / 3746 (1.8)</td>
<td>0.79 (0.61, 1.04)</td>
</tr>
<tr>
<td>Geographic Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US (19%)</td>
<td>83 / 1716 (2.8)</td>
<td>109 / 1693 (3.8)</td>
<td>0.75 (0.56, 1.00)</td>
</tr>
<tr>
<td>Non-US (81%)</td>
<td>244 / 7242 (2.0)</td>
<td>353 / 7359 (2.9)</td>
<td>0.68 (0.57, 0.80)</td>
</tr>
<tr>
<td>Aspirin at Randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (31%)</td>
<td>129 / 2846 (2.7)</td>
<td>164 / 2762 (3.7)</td>
<td>0.75 (0.60, 0.95)</td>
</tr>
<tr>
<td>No (69%)</td>
<td>198 / 6242 (1.9)</td>
<td>298 / 6290 (2.6)</td>
<td>0.66 (0.55, 0.79)</td>
</tr>
</tbody>
</table>

**Note:** The figure 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 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.

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

<table>
<thead>
<tr>
<th>ELIQUIS N=2798</th>
<th>Aspirin N=2780</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>
</tr>
<tr>
<td>Fatal</td>
<td>5 (0.16)</td>
<td>5 (0.16)</td>
<td>0.99 (0.23, 4.29)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>11 (0.34)</td>
<td>11 (0.35)</td>
<td>0.99 (0.39, 2.51)</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(including surgical site)</td>
<td>22 (0.62%)†</td>
<td>18 (0.68%)†</td>
<td>9 (0.60%)†</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High 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>

(Continued)
### Table 3: (Continued)

<table>
<thead>
<tr>
<th>Bleeding Endpoint*</th>
<th>ADVANCE-3 Hip Replacement Surgery</th>
<th>ADVANCE-2 Knee Replacement Surgery</th>
<th>ADVANCE-1 Knee Replacement Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 prior to surgery</td>
<td>First dose 9 to 15 hours prior to surgery</td>
<td>First dose 9 to 15 hours prior to surgery</td>
</tr>
<tr>
<td>Bleed at critical site§</td>
<td>1 (0.04%)</td>
<td>1 (0.07%)</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>126 (8.36%)</td>
</tr>
</tbody>
</table>

---

### Table 4: Adverse Reactions Occurring in ≥1% of Patients Undergoing Hip or Knee Replacement Surgery

<table>
<thead>
<tr>
<th>ELIQUIS, n (%)</th>
<th>Enoxaparin, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=5924</td>
<td>N=5904</td>
</tr>
</tbody>
</table>

- **Nausea**
  - ELIQUIS: 153 (2.6)
  - Enoxaparin: 178 (3.0)
- **Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)**
  - ELIQUIS: 153 (2.6)
  - Enoxaparin: 115 (1.9)
- **Correction**
  - ELIQUIS: 83 (1.4)
  - Enoxaparin: 115 (1.9)
- **Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)**
  - ELIQUIS: 67 (1.1)
  - Enoxaparin: 81 (1.4)
- **Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture-site hematoma, and catheter-site hemorrhage)**
  - ELIQUIS: 54 (0.9)
  - Enoxaparin: 60 (1.0)
- **Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)**
  - ELIQUIS: 50 (0.8)
  - Enoxaparin: 71 (1.2)
- **Aspartate aminotransferase increased**
  - ELIQUIS: 47 (0.8)
  - Enoxaparin: 69 (1.2)
- **Gamma-glutamyltransferase increased**
  - ELIQUIS: 38 (0.6)
  - Enoxaparin: 65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:
- **Blood and lymphatic system disorders:** thrombocytopenia (including platelet count decreases)
- **Vascular disorders:** hypotension (including procedural hypotension)
- **Respiratory, thoracic, and mediastinal disorders:** epistaxis
- **Gastrointestinal disorders:** gastrointestinal hemorrhage (including hematemesis and melena), hematochezia
- **Hepatobiliary disorders:** liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased
- **Renal and urinary disorders:** hematuria (including respective laboratory parameters)
- **Injury, poisoning, and procedural complications:** wound secretion, incision-site hemorrhage (including incision-site hematomata), operative hemorrhage

---

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

<table>
<thead>
<tr>
<th>ELIQUIS</th>
<th>Enoxaparin/Warfarin</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major 15 (0.6) 49 (1.8)</td>
<td>0.31 (0.17, 0.55)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>CRNM* 103 (3.9) 215 (8.0)</td>
<td>0.48 (0.29, 0.79)</td>
<td>p=0.0013</td>
</tr>
<tr>
<td>Major + CRNM* 115 (4.3) 261 (9.7)</td>
<td>0.44 (0.26, 0.74)</td>
<td>p=0.0039</td>
</tr>
<tr>
<td>Minor 313 (11.7) 505 (18.8)</td>
<td>0.39 (0.26, 0.58)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>All 402 (15.0) 676 (25.1)</td>
<td>0.28 (0.20, 0.39)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

* CRNM = clinically relevant nonmajor bleeding.

---

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

<table>
<thead>
<tr>
<th>ELIQUIS</th>
<th>Enoxaparin/Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major 15 (0.6) 49 (1.8)</td>
<td>146 (5.4)</td>
</tr>
<tr>
<td>Contusion 49 (1.8) 97 (3.6)</td>
<td>0.49 (0.30, 0.76)</td>
</tr>
<tr>
<td>Hematuria 46 (1.7) 102 (3.8)</td>
<td>0.45 (0.27, 0.74)</td>
</tr>
<tr>
<td>Menorrhagia 38 (1.4) 20 (0.7)</td>
<td>1.50 (0.82, 2.75)</td>
</tr>
<tr>
<td>Hematoma 35 (1.3) 76 (2.8)</td>
<td>0.46 (0.26, 0.81)</td>
</tr>
<tr>
<td>Epistaxis 32 (1.2) 32 (1.1)</td>
<td>1.00 (0.57, 1.74)</td>
</tr>
<tr>
<td>Rectal hemorrhage 26 (1.0) 39 (1.5)</td>
<td>0.67 (0.40, 1.10)</td>
</tr>
<tr>
<td>Gingival bleeding 26 (1.0) 50 (1.9)</td>
<td>0.52 (0.30, 0.91)</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</th>
<th>ELIQUIS 5 mg bid N=811</th>
<th>Placebo N=826</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>2 (0.2)</td>
<td>1 (0.2)</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.

**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</th>
<th>ELIQUIS 5 mg bid N=811</th>
<th>Placebo N=826</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>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:** hemorraghic anemia
- **Gastrointestinal disorders:** hemorrhage, hemorrhoid hemorrhage, hemorrhagic 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, menstruation, 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 [see Clinical Pharmacology (12.3)].

**7.3 Anticoagulants and Antiplatelet Agents**

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

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

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

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Pregnancy Category B

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

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound apixaban, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

**8.2 Labor and Delivery**

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

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥2.5 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. Mothers 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 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 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the 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 (12.3)]. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.
Propylthiouracil₃ 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 OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding [see Warnings and Precautions (5.2)].

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects. In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

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-h]pyrazin-3-carboxamide. Its molecular formula is C₂₉H₂₃N₅O₅, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:

```
CH₂N₂O₂
O
N
O
N
O
```

Apixaban is a white to pale-yellow powdcr. At physiological pH (12.6-8.8), 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 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 PCCs on Pharmacodynamics of ELIQUIS

There is no clinical experience to reverse bleeding with the use of 4-factor PCC products in individuals who have received ELIQUIS.

Effects of 4-factor PCCs 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 apixaban was coadministered with enoxaparin or naproxen.

Specific Populations

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

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Apixaban 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 D5W 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, C28, C29, C219, and C2. D- 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, 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>Fold Change and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined P-gp and Strong CYP3A4 Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketokonazole 400 mg</td>
<td>C_{max} AUC</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin 500 mg</td>
<td>C_{max} AUC</td>
<td></td>
</tr>
<tr>
<td><strong>Other CYP3A4 and P-gp Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem 360 mg</td>
<td>C_{max} AUC</td>
<td></td>
</tr>
<tr>
<td>Naproxen 500 mg</td>
<td>C_{max} AUC</td>
<td></td>
</tr>
<tr>
<td><strong>Combined P-gp and Strong CYP3A4 Inducer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin 600 mg</td>
<td>C_{max} AUC</td>
<td></td>
</tr>
</tbody>
</table>

Change Relative to Reference

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>Change Relative to Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-Stage Renal Disease $^*$</td>
<td>Normal</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Renal Impairment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe $^*$</td>
<td>Normal</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Moderate</td>
<td>Normal</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Mild</td>
<td>Normal</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Age: ≥65 years/18-40 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;120 kg/65-45 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50 kg/65-45 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Normal</td>
<td>Dosing recommendation cannot be provided</td>
</tr>
<tr>
<td>Mild</td>
<td>Normal</td>
<td>No dose adjustment</td>
</tr>
</tbody>
</table>

Female and African American subjects. No dose adjustment is required based on race/ethnicity.

In all populations, apixaban was not associated with clinically meaningful changes in the pharmacokinetics of the interacting drugs.

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

**Race:** The results across pharmacokinetic studies in normal subjects showed no differences in apixaban pharmacokinetics among White/Caucasian, Asian, and Black/African American subjects. No dose adjustment is required based on race/ethnicity.

**Hemodialysis in ESRD subjects:** Systemic exposure to apixaban administered as a single 5 mg dose in ESRD subjects dosed immediately after the completion of a 4-hour hemodialysis session (post-dialysis) is 38% 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. 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 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 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 greater than or equal to 75 years
- arterial hypertension requiring treatment
- diabetes mellitus
- heart failure $\geq$ New York Heart Association Class 2
- left ventricular ejection fraction $\leq$ 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) 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.

The primary endpoint 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) 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.
embolism in 19% of patients. Concomitant diseases of patients in this study included hypertension 88%, diabetes 25%, congestive heart failure (or left ventricular ejection fraction ≤40%) 35%, and prior myocardial infarction 14%. Patients treated with warfarin in ARISTOTLE had a mean percentage of time in therapeutic range (INR 2.0–3.0) of 62%.

ELIQUIS was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (Table 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>
<thead>
<tr>
<th>ELIQUIS</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause death</td>
<td>n (%/year)</td>
</tr>
<tr>
<td>ELIQUIS</td>
<td>212 (1.27)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>199 (1.19)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.79 (0.66, 0.95)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The primary endpoint was based on the time to first event (one per subject). Component counts are for subjects with any event, not necessarily the first.

Figure 4: Kaplan-Meier Estimate of Time to First Stroke or Systemic Embolism in ARISTOTLE (Intent-to-Treat Population)

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

<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 / 3913 (1.3)</td>
<td>127 / 3998 (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>0.82 (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 / 7403 (1.9)</td>
<td>167 / 7384 (2.2)</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>&gt;3 (30%)</td>
<td>94 / 3758 (2.0)</td>
<td>132 / 3744 (2.6)</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 (3.4)</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 (1.8)</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 / 2659 (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>

Note: The figure 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 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 |
|-----------------------------------------|---------------------------------|-----------------|------------------|
| ELIQUIS N=2807 | Aspirin N=2791 | Hazard Ratio (95% CI) | P-value |
| Stroke or systemic embolism | 51 (1.62%) | 113 (3.63%) | 0.45 (0.32, 0.62) | <0.0001 |
| Stroke | 43 (1.37%) | 97 (3.11%) | 0.40 (0.31, 0.63) | - |
| Ischemic or undetermined | 6 (0.19%) | 9 (0.28%) | 0.67 (0.24, 1.88) | - |
| Hemorrhagic | 2 (0.06%) | 13 (0.41%) | 0.15 (0.03, 0.68) | - |
| MI | 24 (0.76%) | 28 (0.89%) | 0.86 (0.50, 1.48) | - |
| All-cause death | 111 (3.51%) | 140 (4.42%) | 0.79 (0.62, 1.02) | 0.068 |
| Vascular death | 64 (2.65%) | 96 (3.03) | 0.87 (0.65, 1.17) | - |

### 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 replacement surgery (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 renal impairment. In the ADVANCE-3 study, 5407 patients undergoing elective hip replacement surgery were randomized to receive either ELIQUIS® 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. 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 symptomatic and asymptomatic 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 |
|----------------------------------------------------------|------------------|------------------|------------------|
| Events During 35-Day Treatment Period | Relative Risk (95% CI) | P-value |
| ELIQUIS | Enoxaparin | ELIQUIS | Enoxaparin |
| Total VTE All-cause death | 27 (1.39%) | (0.95, 2.02) | 74 (3.86%) | (3.08, 4.83) | 0.36 | (0.22, 0.54) | p<0.0001 |
| All-cause death | 3 (0.11%) | (0.02, 0.35) | 1 (0.04%) | (0.00, 0.24) | - |
| PE | 3 (0.11%) | (0.02, 0.35) | 5 (0.19%) | (0.07, 0.45) | - |
| Symptomatic DVT | 1 (0.04%) | (0.00, 0.24) | 5 (0.19%) | (0.07, 0.45) | - |
| Number of Patients | N=1949 | N=1917 | - |
| Number of Patients | N=2708 | N=2699 | - |
| Number of Patients | N=2196 | N=2190 | - |

| Table 12: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Knee Replacement Surgery |
|----------------------------------------------------------|------------------|------------------|------------------|
| Events During 12-day treatment period | Relative Risk (95% CI) | P-value |
| ELIQUIS | Enoxaparin | ELIQUIS | Enoxaparin |
| All-cause death | 3 (0.19%) | (0.04, 0.59) | 3 (0.19%) | (0.04, 0.59) | 2 (0.13%) | (0.01, 0.52) | 0 (0%) | (0.00, 0.31) |
| PE | 16 (1.0%) | (0.61, 1.64) | 7 (0.44%) | (0.20, 0.93) | 4 (0.26%) | (0.08, 0.70) | 0 (0%) | (0.00, 0.31) |
| Symptomatic DVT | 3 (0.19%) | (0.04, 0.59) | 7 (0.44%) | (0.20, 0.93) | 3 (0.20%) | (0.04, 0.61) | 7 (0.46%) | (0.20, 0.97) |
| Number of Patients | N=1599 | N=1596 | N=1528 | N=1529 |
| Number of Patients | N=1157 | N=1130 | N=976 | N=997 |

| Events during 35-Day Treatment Period | Relative Risk (95% CI) | P-value |
| ELIQUIS | Enoxaparin |
| All-cause death | 104 (8.99%) | (7.47, 10.79) | 100 (8.85%) | (73.3, 106.6) | 1.02 | (0.78, 1.32) | NS |
| PE | 7 (0.56%) | (0.35, 0.93) | 5 (0.32%) | (0.18, 0.76) | 1.05 | (0.75, 1.50) | - |
| Symptomatic DVT | 4 (0.35%) | (0.15, 0.90) | 3 (0.20%) | (0.07, 0.65) | 1.03 | (0.89, 1.20) | NS |
| Number of Patients | N=1125 | N=1120 | N=1192 | N=1199 |
| Number of Patients | N=907 | N=898 | N=782 | N=782 |

Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints. Total VTE includes symptomatic and asymptomatic DVT and PE. Includes symptomatic and asymptomatic DVT.

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 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).

Table 13: Efficacy Results in the AMPLIFY Study

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS N=2609</th>
<th>Enoxaparin/Warfarin N=2635</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE or VTE-related death*</td>
<td>59 (2.3%)</td>
<td>71 (2.7%)</td>
<td>0.84 (0.60, 1.18)</td>
</tr>
<tr>
<td>DVT†</td>
<td>22 (0.8%)</td>
<td>35 (1.3%)</td>
<td>0.62 (0.50, 0.77)</td>
</tr>
<tr>
<td>PE*</td>
<td>27 (1.0%)</td>
<td>25 (0.9%)</td>
<td>1.09 (0.89, 1.34)</td>
</tr>
<tr>
<td>VTE-related death‡</td>
<td>12 (0.4%)</td>
<td>16 (0.6%)</td>
<td>0.76 (0.58, 1.00)</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.
‡ Subjects may have contributed events to multiple endpoints.

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

AMPLIFY-EXT

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

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

The AMPLIFY-EXT study enrolled patients with either an unprovoked DVT or PE at baseline (approximately 92%) or patients with a provoked baseline event and one additional risk factor for recurrence (approximately 8%). However, patients who had experienced multiple episodes of unprovoked DVT or PE were excluded from the AMPLIFY-EXT study.

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

Table 14: Efficacy Results in the AMPLIFY-EXT Study

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS 2.5 mg bid N=840</th>
<th>ELIQUIS 5 mg bid N=813</th>
<th>Placebo N=829</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>32 (3.8%)</td>
<td>34 (4.2%)</td>
<td>56 (6.8%)</td>
<td>0.52 (0.37, 0.75)</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

Table 1:

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Tablet Color/Shape</th>
<th>Tablet Markings</th>
<th>Package Size</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
<td>Yellow, round, biconvex</td>
<td>Debossed with “893” on one side and “5” on the other side</td>
<td>Bottles of 60 Hospital Unit-Dose Blister Package of 100</td>
<td>0003-0893-21</td>
</tr>
<tr>
<td>5 mg</td>
<td>Pink, oval, biconvex</td>
<td>Debossed with “894” on one side and “5” on the other side</td>
<td>Bottles of 60 Hospital Unit-Dose Blister Package of 100</td>
<td>0003-0894-70</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].
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)
ELIQUIS® (apixaban)

- cough up blood or blood clots
- vomit blood or your vomit looks like coffee grounds
- unexpected pain, swelling, or joint pain
- headaches, feeling dizzy or weak

**ELIQUIS is not for patients with artificial heart valves.**

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

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

**What is ELIQUIS?**

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

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

**Who should not take ELIQUIS?**

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

**What should I tell my doctor before taking ELIQUIS?**

Before you take ELIQUIS, tell your doctor if you:
- have kidney or liver problems
- have any other medical condition
- have ever had bleeding problems
- are pregnant or plan to become pregnant. It is not known if ELIQUIS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ELIQUIS passes into your breast milk. You and your doctor should decide if you will take ELIQUIS or breastfeed. You should not do both.

Tell all of your doctors and dentists that you are taking ELIQUIS. They should talk to the doctor who prescribed ELIQUIS for you, before you have any surgery, medical or dental procedure.
Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way ELIQUIS works. Certain medicines may increase your risk of bleeding or stroke when taken with ELIQUIS. See “What is the most important information I should know about ELIQUIS?”

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

How should I take ELIQUIS?

- Take ELIQUIS exactly as prescribed by your doctor.
- Take ELIQUIS twice every day with or without food.
- Do not change your dose or stop taking ELIQUIS unless your doctor tells you to.
- If you miss a dose of ELIQUIS, take it as soon as you remember. Do not take more than one dose of ELIQUIS at the same time to make up for a missed dose.
- If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take ELIQUIS.
- Your doctor will decide how long you should take ELIQUIS. **Do not stop taking it without first talking with your doctor. If you are taking ELIQUIS for atrial fibrillation, stopping ELIQUIS may increase your risk of having a stroke.**

- **Do not run out of ELIQUIS. Refill your prescription before you run out.** When leaving the hospital following hip or knee replacement, be sure that you will have ELIQUIS available to avoid missing any doses.
- If you take too much ELIQUIS, call your doctor or go to the nearest hospital emergency room right away.
- Call your doctor or healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your doctor or healthcare provider may need to check you.

What are the possible side effects of ELIQUIS?

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

- ELIQUIS can cause a skin rash or severe allergic reaction. Call your doctor or get medical help right away if you have any of the following symptoms:
  - chest pain or tightness
  - swelling of your face or tongue
  - trouble breathing or wheezing
  - feeling dizzy or faint

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

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

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

How should I store ELIQUIS?

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

Keep ELIQUIS and all medicines out of the reach of children.
General Information about ELIQUIS

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

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

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

What are the ingredients in ELIQUIS?

Active ingredient: apixaban.

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

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

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Princeton, New Jersey 08543 USA
and
Pfizer Inc
New York, New York 10017 USA

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