Starting on ELIQUIS

a prescription medicine to treat blood clots in the veins of your legs (DVT, deep vein thrombosis) or lungs (PE, pulmonary embolism), and reduce the risk of them occurring again

SEE INSIDE FOR:

- How to take ELIQUIS, including dosing calendar
- ELIQUIS savings and support, including Co-pay Card
- Information on DVT/PE

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.
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 DVT/PE?
Learn about DVT and PE.

Please see selected Important Safety Information below and throughout brochure. Please see U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
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.
What Is ELIQUIS?

ELIQUIS is a prescription blood thinner. If you’ve been diagnosed with deep vein thrombosis (DVT) or pulmonary embolism (PE), your doctor may have prescribed ELIQUIS to treat DVT/PE and reduce the risk of DVT/PE blood clots happening again.

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.

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 Symptoms Continued on Next Page)
WHY ELIQUIS

For the treatment of DVT/PE, ELIQUIS*

PROVEN EFFECTIVE TO TREAT DVT/PE BLOOD CLOTS

HAD SIGNIFICANTLY LESS MAJOR BLEEDING†

*Versus LOVENOX® (enoxaparin) followed by warfarin.

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

(Bleeding Symptoms Continued)

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

Selected Important Safety Information

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.
WHY ELIQUIS

ELIQUIS Proven to Treat DVT/PE

2.7% of the people on LOVENOX®/warfarin and 2.3% of the people on ELIQUIS had a DVT/PE clot. These results are considered comparable.

or 71 out of 2,635 people on LOVENOX®/warfarin had DVT/PE

or 59 out of 2,609 people on ELIQUIS had DVT/PE

ELIQUIS was proven effective to treat DVT/PE blood clots. In this trial, bleeding events were also compared.

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

What Is Major Bleeding?

In the ELIQUIS trials, bleeding was considered major if it was noticeable and had at least one of the following:

■ required a transfusion of 2 or more units of blood
■ occurred in the brain, spine, eye, around the heart, in a joint, or in a muscle and led to damage
■ was fatal

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

Turn the page to learn how the risk of bleeding with ELIQUIS compares to the risk of bleeding with standard treatment, LOVENOX® followed by warfarin.

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.
WHY ELIQUIS

ELIQUIS Had Significantly Less Major Bleeding

Than the Standard Treatment, LOVENOX® Followed by Warfarin

1.8% of the people on LOVENOX®/warfarin and 0.6% of the people on ELIQUIS had major bleeding.

On LOVENOX®/warfarin 1.8%

or 49 out of 2,689 people had major bleeding

On ELIQUIS 0.6%

or 15 out of 2,676 people had major bleeding

Absolute reduction was 1.2% (1.8% – 0.6% = 1.2%). Relative risk reduction was 69%, which means that people on ELIQUIS had a 69% less chance of major bleeding than people on LOVENOX®/warfarin.

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

Understanding the Risk of Another DVT/PE

The second clinical trial was conducted to evaluate whether treating people with ELIQUIS for an additional 12 months after they had completed their initial 6-12 month blood thinner treatment for DVT/PE reduced the risk of a DVT/PE happening again.

More than 1,600 people participated in this study. There were a similar number of people on 2.5 mg of ELIQUIS compared to placebo.

What is a placebo?

A placebo is a pill that contains no medicine.

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.
Compared to placebo,

**ELIQUIS Significantly Reduced the Risk of Another DVT/PE After Initial Treatment**

11.6% of people on placebo had a recurrence of DVT/PE, whereas only 3.8% of those on 2.5 mg of ELIQUIS twice daily had recurrence.

<table>
<thead>
<tr>
<th>On placebo</th>
<th>On ELIQUIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.6%</td>
<td>3.8%</td>
</tr>
<tr>
<td>or 96 out of 829 people had a recurrence</td>
<td>or 32 out of 840 people had a recurrence</td>
</tr>
</tbody>
</table>

Absolute reduction was 7.8% (11.6% – 3.8% = 7.8%). Relative risk reduction was 67%, which means that people on ELIQUIS had a 67% less chance of DVT/PE recurrence than people on placebo.

**Major Bleeding Results:** In the trial, 0.5% (or 4 people) of the 826 people on placebo had major bleeding. 0.2% (or 2 people) of the 840 people who were on 2.5 mg ELIQUIS had major bleeding.

**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.*
### About ELIQUIS, LOVENOX®, and Warfarin

Here’s a look at how taking ELIQUIS compares to taking LOVENOX® and warfarin—two commonly used blood thinners:

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS</th>
<th>LOVENOX®</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How it’s taken</strong></td>
<td>Taken orally twice daily. Can be taken with or without food</td>
<td>Injectable medicine</td>
<td>Taken orally once daily</td>
</tr>
<tr>
<td><strong>Dietary restrictions</strong></td>
<td>No known dietary restrictions</td>
<td>No known dietary restrictions</td>
<td>Certain dietary restrictions</td>
</tr>
<tr>
<td><strong>Routine INR blood testing</strong></td>
<td>Does not require routine INR blood testing</td>
<td>Does not require routine INR blood testing</td>
<td>Requires routine INR testing to check if levels are within the target range. If they’re not, your physician may adjust the dose</td>
</tr>
</tbody>
</table>

Always take ELIQUIS exactly as prescribed by your doctor.

### 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.

Please see additional Important Safety Information throughout brochure and [U.S. Full Prescribing Information](ELIQUIS.com), 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 it either with or without food and store at room temperature. There are no restrictions or “watch outs” for foods like green leafy vegetables.

No special handling required.

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

Don’t change your dose or stop taking ELIQUIS without first talking with your doctor. Stopping ELIQUIS increases your risk of having a stroke if you are taking ELIQUIS for atrial fibrillation not caused by a heart valve problem.

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.

If you have to stop taking ELIQUIS, your doctor may prescribe another medicine to help prevent a blood clot from forming.

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.

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.
Your ELIQUIS Dosage

Depending on why you’re taking ELIQUIS, your dose may be different. For any dose, make sure you follow your doctor’s instructions when taking ELIQUIS.

For Treating DVT/PE

If you’re taking ELIQUIS because you’ve been diagnosed with DVT/PE, you will need to change your dose of ELIQUIS after 7 days. See the boxes below to learn about your starting and continuing doses.

First 7 days

Two 5-mg tablets twice a day

After 7 days

One 5-mg tablet twice a day
If you're taking ELIQUIS (apixaban) for the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE), there is an important dosing change after 7 days. Use the calendar below to help keep track of your ELIQUIS dosage during the first two weeks of treatment. Please note, treatment with ELIQUIS may continue beyond 2 weeks. Remember to always take ELIQUIS as prescribed by your doctor. Do not stop taking ELIQUIS without talking to the doctor who prescribed it for you.

### First 7 Days: take two 5-mg pills in the morning and two at night

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>☀️</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>🌙</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

### After 7 Days: take one 5-mg pill in the morning and one at night

<table>
<thead>
<tr>
<th>Day</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>☀️</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>🌙</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**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 Page 20)

**After 14 days, continue therapy as discussed with your doctor.**

**Questions?**

If you have questions, review your prescription with your healthcare provider to make sure you take the correct dosage strength and number of tablets.

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
For Reducing Risk of Recurrent DVT/PE After Initial Therapy

If you’re taking ELIQUIS (apixaban) to reduce the risk of recurrence after your initial 6 months of DVT/PE treatment, see the box below to learn about your extended therapy dose. Always be sure to take ELIQUIS exactly as prescribed by your doctor.

### After at least 6 months of DVT/PE treatment

<table>
<thead>
<tr>
<th>Sun</th>
<th>Moon</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

One 2.5-mg tablet twice a day

---

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.

---

Continue Talking With Your Doctor

As you begin taking ELIQUIS, 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/discussion](http://www.ELIQUIS.com/discussion).

---

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

---

Please see additional Important Safety Information throughout brochure and [U.S. Full Prescribing Information](http://www.ELIQUIS.com), including [Boxed WARNINGS](http://www.ELIQUIS.com) and [Medication Guide](http://www.ELIQUIS.com), or visit [ELIQUIS.com](http://www.ELIQUIS.com).
How Can I Get Savings & Support?

EXPLORE THIS SECTION TO LEARN ABOUT:

- Signing up for ELIQUIS 360 Support
- Activating your Co-pay Card, if eligible
- Getting help to understand your insurance coverage

Please see Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
How Can I Get Savings & Support?

If you’re living with DVT/PE, it helps to have ongoing support. ELIQUIS 360 Support is here to help.

360 Support Informational Materials Include:

- Interesting facts about DVT/PE
- Valuable tips and guidance for living with DVT/PE

Selected Important Safety Information

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
- 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.
**Sign up for ELIQUIS 360 Support**

Need help with co-pays or determining your prescription coverage? Want to learn more about DVT/PE and ELIQUIS? ELIQUIS 360 Support is here to help. Sign up to receive newsletters and emails by:

- Visiting [www.ELIQUIS.com/newsletters](http://www.ELIQUIS.com/newsletters)
- 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)

---

**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](http://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

---

**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.

---

Please see additional Important Safety Information throughout brochure and [U.S. Full Prescribing Information](http://www.ELIQUIS.com), including Boxed WARNINGS and Medication Guide, or visit [ELIQUIS.com](http://www.ELIQUIS.com).

---

**Eliquis**

(apixaban) tablets 5mg, 2.5mg
Representatives Can Also Help With:

**Prior authorization:** If your insurance plan needs prior authorization before approving coverage of ELIQUIS, 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

**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**.
What Are DVT and PE?

DVT is a blood clot in a deep vein – usually in the lower legs, thighs, or pelvis – that limits the flow of blood in veins. Sometimes a DVT blood clot can break free and travel to the lungs. This is known as a PE. A PE blood clot can limit the flow of blood in the lungs and can even cause sudden death. DVT/PE can happen more than once.

What Are Some Symptoms of DVT/PE?

Symptoms of DVT may include:
- Swelling in the leg or around a vein in the leg
- Pain or tenderness felt when standing or walking
- Redness around the affected area

Symptoms of PE may include:
- Difficulty breathing
- Faster than normal or irregular heartbeat
- Chest pain
- Coughing up blood
- Very low blood pressure, light-headedness, or fainting

It’s possible that people with DVT and/or PE may experience no symptoms at all.

If you have any of these symptoms for DVT and/or PE, seek immediate medical attention.

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

Who Is at Risk for Having Another DVT or PE?

If you’ve had deep vein thrombosis (DVT) or pulmonary embolism (PE), you may be at risk of having another case of DVT or PE. That’s known as a “recurrence.” Each person’s risk of recurrence varies. Your risk of recurrence is higher if the DVT/PE event was not triggered by a known risk factor.

Some examples of known risk factors include taking a long plane ride or car trip, having a major surgery, or taking certain medications.

How Common Is Recurrence?

33%

It’s estimated that one out of three people with DVT/PE have a recurrence within 10 years.

Keep in Mind:

- The risk of recurrence is highest within the first year after the initial DVT/PE
- In some cases, the risk of recurrence can remain years after the first event
- Treatment can help reduce the risk of recurrence

If you think you’re experiencing another DVT/PE, it is important that you go to your doctor or to the hospital right away.

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.

Watch Dr. Why explain the risk of another DVT/PE at www.ELIQUIS.com/risk

Please see additional Important Safety Information throughout brochure and U.S. Full Prescribing Information, including Boxed WARNINGS and Medication Guide, or visit ELIQUIS.com.
Use this page to write out questions to ask your doctor or take notes about ELIQUIS® (apixaban)

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

Learn more about your condition and ELIQUIS

Sign up for 360 Support

Or, visit www.moblkit.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.
**FULL PRESCRIBING INFORMATION: CONTENTS**

**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)

---

**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)

---

**WARNINGS AND PRECAUTIONS**

- Active pathological bleeding (4)
- Severe hypersensitivity to ELIQUIS (apixaban) (4)

**CONTRAINDICATIONS**

- ELIQUIS can cause serious, potentially fatal, bleeding. Promptly evaluate signs and symptoms of blood loss. An agent to reverse the anti-factor Xa activity of apixaban is available. (5.2)
- Prosthetic heart valves: ELIQUIS use not recommended. (5.4)

**ADVERSE REACTIONS**

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

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

**DRUG INTERACTIONS**

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

**USE IN SPECIFIC POPULATIONS**

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2018

---

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use ELIQUIS safely and effectively. See full prescribing information for ELIQUIS.

ELIQUIS® (apixaban) tablets, for oral use

---

**WARNINGS AND PRECAUTIONS (5.2)**

---

**RECENT MAJOR CHANGES**

---

**INDICATIONS AND USAGE**

---

**DOSE FORMS AND STRENGTHS**

---

**DRUG INTERACTIONS**

---

**USE IN SPECIFIC POPULATIONS**

---

**NONCLINICAL TOXICOLOGY**

---

**CLINICAL STUDIES**

---

**HOW SUPPLIED/STORAGE AND HANDLING**

---

**PATIENT COUNSELING INFORMATION**

---

* Sections or subsections omitted from the full prescribing information are not listed.
1 INDICATIONS AND USAGE

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

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

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

ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

1.3 Treatment of Deep Vein Thrombosis

ELIQUIS is indicated for the treatment of DVT.

1.4 Treatment of Pulmonary Embolism

ELIQUIS is indicated for the treatment of PE.

1.5 Reduction in the Risk of Recurrence of DVT and PE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

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

The recommended dose of ELIQUIS for most patients is 5 mg taken orally twice daily. The recommended dose of ELIQUIS is 2.5 mg twice daily in patients with at least two of the following characteristics:

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

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

- In patients undergoing hip replacement surgery, the recommended duration of treatment is 35 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.

Treatment of DVT and PE

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

2.2 Missed Dose

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

2.3 Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding [see Warnings and Precautions (5.2)]. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

2.4 Converting from or to ELIQUIS

Switching from warfarin to ELIQUIS: Warfarin should be discontinued and ELIQUIS started when the international normalized ratio (INR) is below 2.0. Switching from ELIQUIS to warfarin: ELIQUIS affects INR, so that initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue ELIQUIS and begin both a parenteral anticoagulant and warfarin at the time the next dose of ELIQUIS would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

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

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

2.5 Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose by 50% when ELIQUIS is coadministered with drugs that are combined P-glycoprotein (P-gp) and strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketocanazole, itraconazole, rifampin) [see Clinical Pharmacology (12.3)]. In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors [see Drug Interactions (7.1)].

2.6 Administration Options

For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally [see Clinical Pharmacology (12.3)]. Alternatively, ELIQUIS tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube [see Clinical Pharmacology (12.3)]. Crushed ELIQUIS tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [see Dosage and Administration (2.4) and Clinical Studies (14.1)].

5.2 Bleeding

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

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

Reversal of Anticoagulant Effect

An agent to reverse the ant-factor Xa activity of apixaban is available. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Prothrombin complex concentrate (PCC), activated or prothrombin complex concentrate or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies [see Clinical Pharmacology (12.2)]. When PCCs are used, monitoring for the anticoagulant 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 Thrombolysis or Pulmonary Embolectomy

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).
‡ Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intracranial, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.
§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.
** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.
ELIQUIS® (apixaban)

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were 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 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

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: (Continued)

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

<table>
<thead>
<tr>
<th>Bleeding Endpoint*</th>
<th>ADVANCE-3 Hip Replacement Surgery</th>
<th>ADVANCE-2 Knee Replacement Surgery</th>
<th>ADVANCE-1 Knee Replacement Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ELIQUIS 2.5 mg po bid 35±3 days</td>
<td>Enoxaparin 40 mg sc 35±3 days</td>
<td>ELIQUIS 2.5 mg po bid 12±2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12±2 days</td>
<td>Enoxaparin 40 mg sc 12±2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12±2 days</td>
<td>Enoxaparin 30 mg sc 12±2 days</td>
</tr>
<tr>
<td></td>
<td>First dose 12 to 24 hours after 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></td>
<td></td>
<td>First dose 12 to 24 hours after surgery</td>
<td>First dose 12 to 24 hours after surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>First dose 12 to 24 hours after surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleed at critical site†</td>
<td>1 (0.04%)</td>
<td>1 (0.04%)</td>
<td>2 (0.13%)</td>
</tr>
<tr>
<td>Major + CRNM‡</td>
<td>129 (4.83%)</td>
<td>134 (5.04%)</td>
<td>72 (4.77%)</td>
</tr>
<tr>
<td>All</td>
<td>313 (11.71%)</td>
<td>334 (12.56%)</td>
<td>126 (8.36%)</td>
</tr>
</tbody>
</table>

All bleeding criteria included surgical site bleeding.

*Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post-surgery).

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

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

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

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

CRNM = clinically relevant nonmajor bleeding.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

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

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS, n (%)</th>
<th>Enoxaparin, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=5924</td>
<td>153 (2.6%)</td>
<td>178 (3.0%)</td>
</tr>
<tr>
<td>N=5904</td>
<td>159 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)</td>
<td>153 (2.6%)</td>
<td>178 (3.0%)</td>
</tr>
<tr>
<td>Contusion</td>
<td>83 (1.4%)</td>
<td>115 (1.9%)</td>
</tr>
<tr>
<td>Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)</td>
<td>67 (1.1%)</td>
<td>81 (1.4%)</td>
</tr>
<tr>
<td>Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture-site hematoma, and catheter-site hemorrhage)</td>
<td>54 (0.9%)</td>
<td>60 (1.0%)</td>
</tr>
<tr>
<td>Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)</td>
<td>50 (0.8%)</td>
<td>71 (1.2%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>47 (0.8%)</td>
<td>69 (1.2%)</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>38 (0.6%)</td>
<td>65 (1.1%)</td>
</tr>
</tbody>
</table>

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of >0.1% to <1%:

**Blood and lymphatic system disorders:** thrombocytopenia (including platelet count decreases)

**Vascular disorders:** hypotension (including procedural hypotension)

**Respiratory, thoracic, and mediastinal disorders:** epistaxis

**Gastrointestinal disorders:** gastrointestinal hemorrhage (including hematemesis and melena), hematocolitis

**Hepatobiliary disorders:** liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

**Renal and urinary disorders:** hematuria (including respective laboratory parameters)

**Injury, poisoning, and procedural complications:** wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Table 5: Bleeding Results in the AMPLIFY Study

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

CRNM = clinically relevant nonmajor bleeding.

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

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

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS N=2676</th>
<th>Enoxaparin/Warfarin N=2689</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>77 (2.9)</td>
<td>146 (5.4)</td>
</tr>
<tr>
<td>Contusion</td>
<td>49 (1.8)</td>
<td>97 (3.6)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>46 (1.7)</td>
<td>102 (3.8)</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>38 (1.4)</td>
<td>30 (1.1)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>35 (1.3)</td>
<td>76 (2.8)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>32 (1.2)</td>
<td>31 (1.2)</td>
</tr>
<tr>
<td>Rectal hemorrhage</td>
<td>26 (1.0)</td>
<td>39 (1.5)</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>26 (1.0)</td>
<td>50 (1.8)</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.
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 cilostogrel, 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 drug, 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 ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

8.3 Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose). It is not known whether these concentrations will lead to similar stroke reduction activity similar to those observed in the ARISTOTLE study [see Clinical Pharmacology (12.3)].

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.

<table>
<thead>
<tr>
<th>Table 7: Bleeding Results in the AMPLIFY-EXT Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIQUIS 2.5 mg bid N=840</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Major</td>
</tr>
<tr>
<td>CRNM*</td>
</tr>
<tr>
<td>Major + CRNM</td>
</tr>
<tr>
<td>Minor</td>
</tr>
<tr>
<td>All</td>
</tr>
</tbody>
</table>

* CRNM = clinically relevant nonmajor bleeding.

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

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

<table>
<thead>
<tr>
<th>Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIQUIS 2.5 mg bid N=840</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Epistaxis</td>
</tr>
<tr>
<td>Hematuria</td>
</tr>
<tr>
<td>Hematoma</td>
</tr>
<tr>
<td>Contusion</td>
</tr>
<tr>
<td>Gingival bleeding</td>
</tr>
</tbody>
</table>
Propylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis [see Dosage and Administration (2.1)]. Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis [see Clinical Pharmacology (12.2)].

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

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

11 DESCRIPTION

ELIQUIS (apixaban), a factor Xa (FXa) inhibitor, is chemically described as 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide. Its molecular formula is C25H25N5O4, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:

```
H3N
O
N
O
H,CO
```

Apixaban is a white to pale-yellow powder. At physiological pH (1.2-6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban. The Rotachrom® Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program. 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.
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>Combined P-gp and Strong CYP3A4 Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole 400 mg</td>
<td>$C_{\text{min}}$</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin 500 mg</td>
<td>$C_{\text{AUC}}$</td>
<td></td>
</tr>
<tr>
<td>Other CYP3A4 and P-gp Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem 360 mg</td>
<td>$C_{\text{max}}$</td>
<td></td>
</tr>
<tr>
<td>Naproxen 500 mg</td>
<td>$C_{\text{AUC}}$</td>
<td></td>
</tr>
<tr>
<td>Combined P-gp and Strong CYP3A4 Inducer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin 600 mg</td>
<td>$C_{\text{max}}$</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{AUC}}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In dedicated studies conducted in healthy subjects, famotidine, atenolol, prasugrel, and enoxaparin did not meaningfully alter the pharmacokinetics of 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>Fold Change and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-Stage Renal Disease†/Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Impairment: Severe†/Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Impairment: Moderate/Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Impairment: Mild/Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: ≥65 years/18-40 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight: ≥120 kg/65-64.5 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight: ≤50 kg/65-64.5 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment: Moderate/Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment: Mild/Normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 ESRD subjects treated with intermittent hemodialysis; reported PK findings are following single dose of apixaban post hemodialysis.

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

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

Hemodialysis in ESRD subjects: Systemic exposure to apixaban administered as a single 5 mg dose in ESRD subjects dosed immediately after the completion of a 4-hour hemodialysis session (post-dialysis) is 36% higher when compared to subjects with normal renal function (Figure 3). The systemic exposure to apixaban administered 2 hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min is 17% higher compared to those with normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min. The systemic exposure of apixaban is 14% lower on dialysis when compared to not on dialysis.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Apixaban administered to female rats at doses up to 1000 mg/kg/day from implantation through the end of lactation produced no adverse findings in male offspring (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 ≥New York Heart Association Class 2
- left ventricular ejection fraction ≤40%

The primary objective of ARISTOTLE was to determine whether ELIQUIS 5 mg twice daily (or 2.5 mg twice daily) was effective (noninferior to warfarin) in reducing the risk of stroke (ischemic or hemorrhagic) and systemic embolism. Superiority of ELIQUIS to warfarin was also examined for the primary endpoint (rate of stroke and systemic embolism) during the on-dialysis and off-dialysis periods.

A total of 18,201 patients were randomized and followed on study treatment for a median of 89 weeks. Forty-three percent of patients were vitamin K antagonist (VKA) “naive,” defined as having received ≤30 consecutive days of treatment with warfarin or another VKA before entering the study. The mean age was 69 years and the mean CHADS2 score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk) was 2.1. The population was 65% male, 83% Caucasian, 14% Asian, and 1% Black. There was a history of stroke, TIA, or non-CNS systemic
embolism in 19% of patients. Concomitant diseases of patients in this study included hypertension 88%, diabetes 25%, congestive heart failure (or left ventricular ejection fraction <40%) 35%, and prior myocardial infarction 14%. Patients treated with warfarin in ARISTOTLE had a mean percentage of time in therapeutic range (INR 2.0-3.0) of 62%.

ELIQUIS was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (Table 9 and Figure 4). Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs.

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

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

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

Number of Subjects at Risk
ELIQUIS 9120 8726 8440 6951 3464 1754 600
Warfarin 9081 8620 8301 5972 3405 1768 572

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

In ARISTOTLE, the results for the primary efficacy endpoint were generally consistent across most major subgroups including weight, CHADS 2 score (a scale from 0 to 6 used to predict risk of stroke in patients with AF, with higher scores predicting greater risk), prior warfarin use, level of renal impairment, geographic region, and aspirin use at randomization (Figure 5).

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

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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ELIQUIS 2.5 mg po bid N=2807</th>
<th>Aspirin 325 mg po N=2791</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>51 (1.62)</td>
<td>113 (3.63)</td>
<td>0.45 (0.32, 0.62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>43 (1.57)</td>
<td>97 (3.11)</td>
<td>0.67 (0.31, 1.06)</td>
<td>-</td>
</tr>
<tr>
<td>Ischemic or undetermined</td>
<td>6 (0.21)</td>
<td>9 (0.28)</td>
<td>0.78 (0.34, 1.79)</td>
<td>-</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>2 (0.07)</td>
<td>13 (0.46)</td>
<td>0.15 (0.03, 0.72)</td>
<td>-</td>
</tr>
<tr>
<td>Ml</td>
<td>24 (0.76)</td>
<td>28 (0.89)</td>
<td>0.86 (0.50, 1.48)</td>
<td>-</td>
</tr>
<tr>
<td>All-cause death</td>
<td>111 (3.51)</td>
<td>140 (4.42)</td>
<td>0.79 (0.62, 1.02)</td>
<td>0.068</td>
</tr>
<tr>
<td>Vascular death</td>
<td>84 (2.65)</td>
<td>96 (3.03)</td>
<td>0.87 (0.65, 1.17)</td>
<td>-</td>
</tr>
</tbody>
</table>

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

The clinical evidence for the effectiveness of ELIQUIS is derived from the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical trials in adult patients undergoing elective hip (ADVANCE-3) or knee (ADVANCE-2 and ADVANCE-1) replacement surgery. A total of 11,659 patients were randomized in 3 double-blind, multi-national studies. Included in this total were 1866 patients age 75 or older, 1161 patients with low body weight (≤60 kg), 7258 patients with Body Mass Index ≥33 kg/m<sup>2</sup>, 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 2.5 mg orally twice daily or enoxaparin 40 mg subcutaneously once daily. The first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Treatment duration was 32 to 38 days.

In patients undergoing elective knee replacement surgery, ELIQUIS 2.5 mg orally twice daily was compared to enoxaparin 40 mg subcutaneously once daily (ADVANCE-2, N=3057) or enoxaparin 30 mg subcutaneously every 12 hours (ADVANCE-1, N=3195). In the ADVANCE-2 study, the first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. In the ADVANCE-1 study, both ELIQUIS and enoxaparin were initiated 12 to 24 hours post surgery. Treatment duration in both ADVANCE-2 and ADVANCE-1 was 10 to 14 days.

In all 3 studies, the primary endpoint was a composite of adjudicated 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.
ELIQUIS® (apixaban)

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

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

AMPLIFY

The primary objective of AMPLIFY was to determine whether ELIQUIS was noninferior to enoxaparin/warfarin for the incidence of recurrent VTE (venous thromboembolism) or VTE-related death. Patients with an objectively confirmed symptomatic DVT and/or PE were randomized to treatment with ELIQUIS 10 mg twice daily orally for 6 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 2.5 mg bid N=2635</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></td>
</tr>
<tr>
<td>PE*</td>
<td>27 (1.0%)</td>
<td>25 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>VTE-related death†</td>
<td>12 (0.4%)</td>
<td>16 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>VTE or all-cause death</td>
<td>84 (3.2%)</td>
<td>104 (4.0%)</td>
<td>0.82 (0.61, 1.08)</td>
</tr>
<tr>
<td>VTE or CV-related death</td>
<td>61 (2.3%)</td>
<td>72 (2.7%)</td>
<td>0.80 (0.57, 1.11)</td>
</tr>
</tbody>
</table>

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

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

AMPLIFY-EXT

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

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

The AMPLIFY-EXT study enrolled patients with either an unprovoked DVT or PE at baseline (approximately 92%) or patients with a provoked baseline event and an 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>Recurrent VTE or VTE-related death</td>
<td>32 (3.8%)</td>
<td>34 (4.2%)</td>
<td>96 (11.6%)</td>
<td>0.33 (0.22, 0.48)</td>
</tr>
<tr>
<td>DVT*</td>
<td>19 (2.3%)</td>
<td>28 (3.4%)</td>
<td>72 (8.7%)</td>
<td>0.23 (0.12, 0.42)</td>
</tr>
<tr>
<td>PE*</td>
<td>23 (2.7%)</td>
<td>25 (3.1%)</td>
<td>37 (4.5%)</td>
<td>1.15 (0.71, 1.88)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>22 (2.6%)</td>
<td>25 (3.1%)</td>
<td>33 (4.0%)</td>
<td>1.04 (0.65, 1.67)</td>
</tr>
</tbody>
</table>

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

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

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

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

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

Advise patients of the following:

• Not to discontinue ELIQUIS without talking to their physician first.

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

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

• If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas [see Warnings and Precautions (5.3)]. If any of these symptoms occur, advise the patient to seek emergent medical attention.

• To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS [see Use in Specific Populations (8.1, 8.3)].

• How to take ELIQUIS if they cannot swallow, or require a nasogastric tube [see Dosage and Administration (2.6)].

• What to do if a dose is missed [see Dosage and Administration (2.2)].

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

Rotachrom® is a registered trademark of Diagnostica Stago.
ELIQUIS® (apixaban)

MEDICATION GUIDE

ELIQUIS® (ELL eh kwiss)
(apixaban)
tablets

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

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

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

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

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

  You may have a higher risk of bleeding if you take ELIQUIS and take other medicines that increase your risk of bleeding, including:
  
  - aspirin or aspirin-containing products
  - long-term (chronic) use of nonsteroidal anti-inflammatory drugs (NSAIDs)
  - warfarin sodium (COUMADIN®, JANTOVEN®)
  - any medicine that contains heparin
  - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
  - other medicines to help prevent or treat blood clots

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

While taking ELIQUIS:

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

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

- unexpected bleeding, or bleeding that lasts a long time, such as:
  - unusual bleeding from the gums
  - nosebleeds that happen often
  - menstrual bleeding or vaginal bleeding that is heavier than normal
- bleeding that is severe or you cannot control
- red, pink, or brown urine
- red or black stools (looks like tar)
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.
ELIQUIS® (apixaban)

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.

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

COUMADIN® is a registered trademark of Bristol-Myers Squibb Pharma Company. All other trademarks are property of their respective companies.

Revised July 2016

432US1801820-01-01