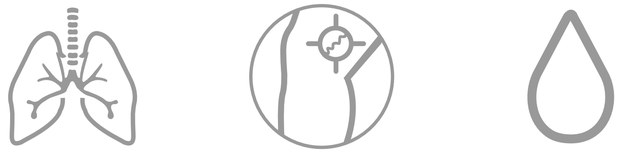

AMPLIFY: a randomized, double-blind, phase 3 trial for the treatment of venous thromboembolism (VTE)[1,2]

INDICATION

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

SELECTED IMPORTANT SAFETY INFORMATION

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

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

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

- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of ELIQUIS and neuraxial procedures is not known

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

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

Continue

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699-708.

Please see **Important Safety Information** throughout and Full Prescribing Information, including **Boxed WARNINGS**, or visit ELIQUIS.com.

Eliquis® (apixaban) tablets 5mg 2.5mg

AMPLIFY was a randomized double-blind, phase 3 noninferiority trial[1,2]

Primary objective:

To determine whether ELIQUIS was noninferior to enoxaparin/warfarin for the incidence of recurrent VTE* or VTE-related death

IN PATIENTS WITH DVT AND/OR PE

RANDOMIZED, DOUBLE-BLIND
N=5400

ELIQUIS
10 mg orally twice daily for 7 days followed by 5 mg orally twice daily for 6 months
n=2693

enoxaparin/warfarin
enoxaparin 1 mg/kg subcutaneously twice daily for at least 5 days (until INR ≥2) followed by warfarin (target INR range 2.0-3.0) orally for 6 months
n=2707

Primary efficacy endpoint: recurrent VTE* or VTE-related death

Primary safety endpoint: major bleeding

- Approximately 90% of patients had an unprovoked DVT or PE at baseline, and 10% of patients with a provoked DVT or PE were required to have an additional ongoing risk factor, which included a previous episode of DVT or PE, immobilization, history of cancer, active cancer, and known prothrombotic genotype[1]
- Patients were allowed to enter the study with or without prior parenteral anticoagulation (up to 48 hours)[1]

Major bleeding was defined as clinically overt bleeding accompanied by ≥1 of the following[2,3]: a decrease in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal; and fatal bleeding.

BASELINE CHARACTERISTICS +

Select inclusion criteria: objectively confirmed, symptomatic proximal DVT and/or PE.

Select exclusion criteria: 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, or cancer and for whom long-term treatment with low-molecular-weight heparin was planned.

DVT=deep vein thrombosis; INR=international normalized ratio; PE=pulmonary embolism.
*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).

SELECTED IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699-708. **3.** Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.

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AMPLIFY w

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For the treatment of DVT/PE,

ELIQUIS® (apixaban) was studied across various patient subgroups[1]

Select clinical characteristics represented in AMPLIFY patient population[1]	ELIQUIS n=2691		enoxaparin/warfarin n=2704	
Extensive PE at baseline*	13.3%	n=357	12.1%	n=326
Weight ≥100 kg	19.4%	n=522	19.2%	n=518
Moderate renal impairment (CrCl >30 to ≤50 mL/min)	6.0%	n=161	5.5%	n=148
Severe renal impairment (CrCl ≤30 mL/min)	0.5%	n=14	0.6%	n=15
Previous VTE	17.2%	n=463	15.1%	n=409
Active cancer[2†‡]	3.3%	n=88	3.0%	n=81

†Baseline values taken from the journal publication Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost.* 2015;13:2187-2191.

CrCl=creatinine clearance.
*Pulmonary embolism was defined as extensive if there were 2 or more lobes involving 50% or more of the vasculature for each lobe.
‡Active cancer was defined as cancer diagnosed or treated within the past 6 months without the necessity for low-molecular-weight heparin treatment.

References: 1. Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699-708. **2.** Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost*. 2015;13(12):2187-2191.

For the treatment of DVT/PE,

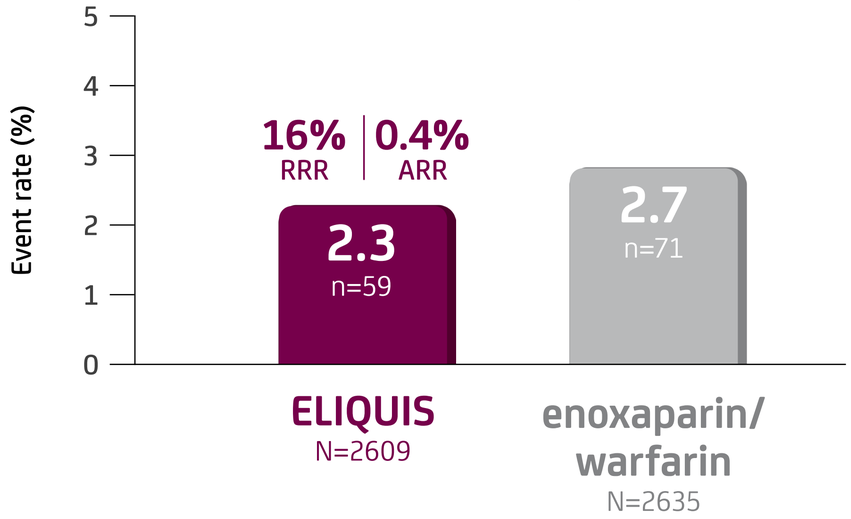
ONLY ELIQUIS demonstrated BOTH comparable efficacy AND superiority in major bleeding events vs enoxaparin/warfarin[1]

COMPARABLE

In VTE*/VTE-related death

RR=0.84 (95% CI: 0.60, 1.18)

P<0.0001 for noninferiority



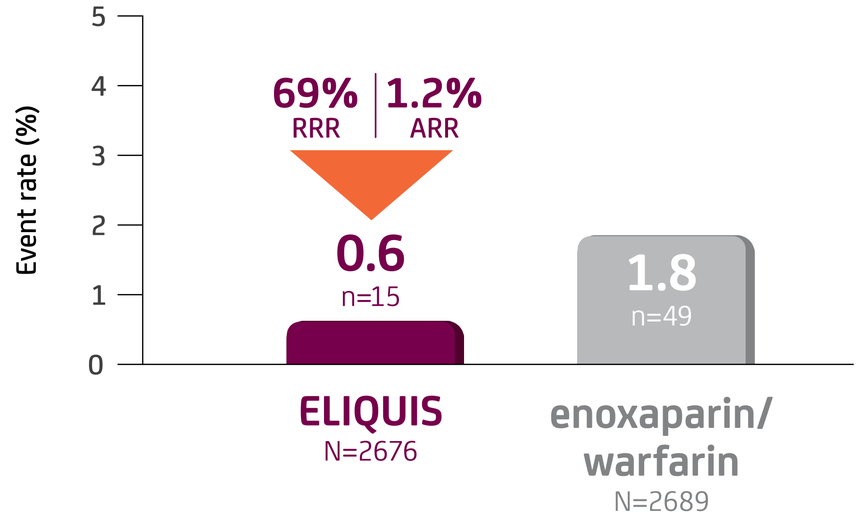
Primary efficacy endpoint

SUPERIOR

Major bleeding†

RR=0.31 (95% CI: 0.17, 0.55)

P<0.0001



Primary safety endpoint

Consistent efficacy and rates of major bleeding across key patient subgroups[2]

Renal impairment

Age

Weight

Gender

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

- In AMPLIFY, discontinuation rate due to bleeding events: 0.7% with ELIQUIS vs 1.7% with enoxaparin/warfarin
- In AMPLIFY, the most commonly observed adverse reactions in patients treated with ELIQUIS (incidence ≥1%) were epistaxis, contusion, hematuria, menorrhagia, hematoma, hemoptysis, rectal hemorrhage, and gingival bleeding

ARR=absolute risk reduction; CI=confidence interval; HR=hazard ratio; RRR=relative risk reduction.
*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).
†Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

SELECTED IMPORTANT SAFETY INFORMATION: WARNINGS AND PRECAUTIONS

- Increased Risk of Thrombotic Events after Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

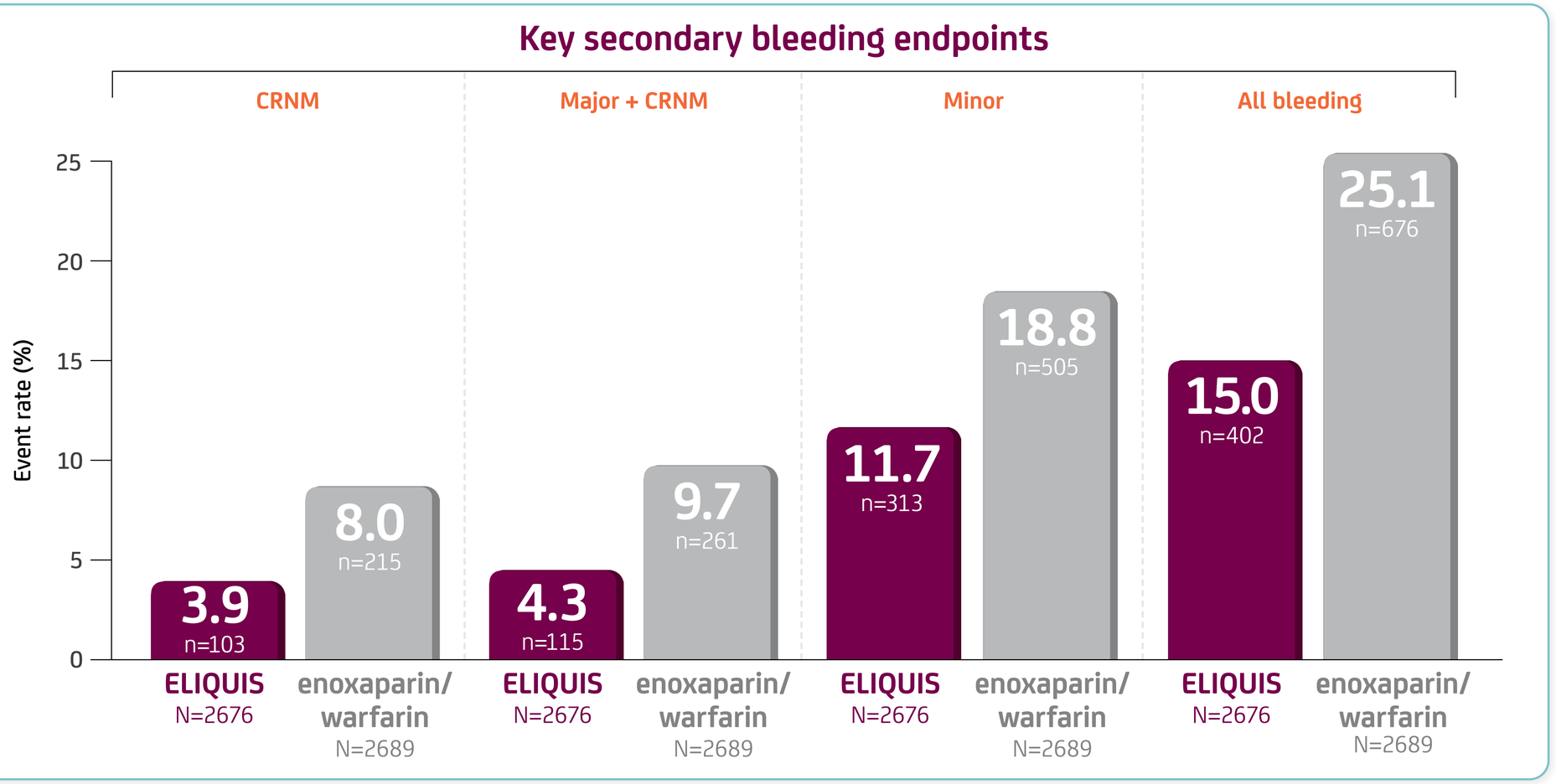
References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808.

Please see **Important Safety Information** throughout and Full Prescribing Information, including **Boxed WARNINGS**, or visit ELIQUIS.com.

Eliquis® (apixaban) tablets 5mg 2.5mg

For the treatment of DVT/PE,

ELIQUIS demonstrated fewer bleeding events across key secondary endpoints, including CRNM[1]*



- CRNM bleeding was defined as overt bleeding not meeting the criteria for major bleeding, but associated with at least 1 of the following[2]:
  - Medical intervention
  - Contact with an HCP
  - Interruption of the study drug
  - Discomfort or impairment in carrying out activities of daily life

CRNM BLEEDING EXAMPLES +

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

- **In AMPLIFY, discontinuation rate due to bleeding events: 0.7% with ELIQUIS vs 1.7% with enoxaparin/warfarin[1]**

CRNM=clinically relevant nonmajor; HCP=health care provider.
*Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

SELECTED IMPORTANT SAFETY INFORMATION: WARNINGS AND PRECAUTIONS (cont'd)

- Bleeding Risk: ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.

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Eliquis® (apixaban) tablets 5mg 2.5mg

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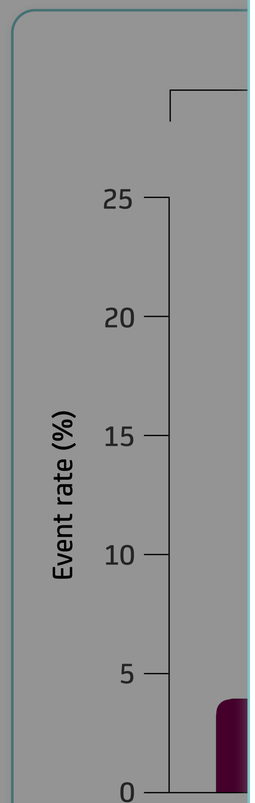

RNM[1]*

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Select examples of CRNM bleeding[1]

- Any bleeding leading to hospitalization
- Macroscopic gastrointestinal hemorrhage, including at least one episode of melena or hematemesis, if clinically apparent with positive results on a fecal occult blood test
- Epistaxis lasting >5 minutes, that was repetitive, or that led to an intervention
- Macroscopic, spontaneous hematuria or hematuria lasting >24 hours after instrumentation of the urogenital tract
- Hemoptysis (if more than a few speckles in the sputum and not occurring within the context of PE)
- Any bleeding compromising hemodynamics
- Any other bleeding type considered to have clinical consequences for a patient

Reference: 1. Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808.

- **In AMPLIFY, d**

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SELECTED IMP

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Please see **Important Safety Information** throughout and **Full Prescribing Information**, including **Boxed WARNINGS**, or visit **ELIQUIS.com**.

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For the treatment of DVT/PE,

ELIQUIS demonstrated consistent efficacy and rates of major bleeding across key patient subgroups[1,2]

In AMPLIFY, an analysis of the primary efficacy (VTE*/VTE-related death) and primary safety (major bleeding) endpoints by key subgroups included:

- Level of renal impairment
- Age
- Gender
- Weight

PRIMARY EFFICACY FOREST PLOT +

PRIMARY SAFETY FOREST PLOT +

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).

SELECTED IMPORTANT SAFETY INFORMATION: WARNINGS AND PRECAUTIONS (cont'd)

- Spinal/Epidural Anesthesia or Puncture: Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

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

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

References: 1. Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.
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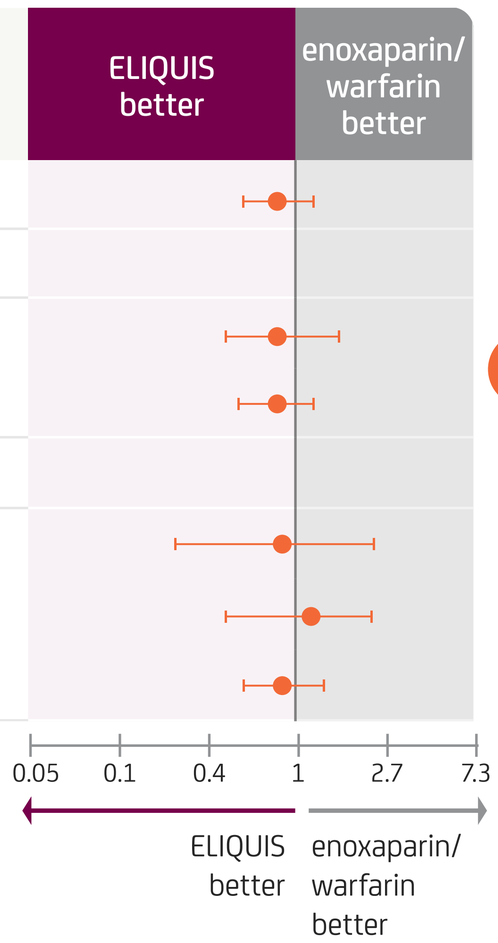
EFFICACY

For the treatment of DVT/PE,

Rates of VTE*/VTE-related death across key patient subgroups[1-3]

n of events/N of patients

	ELIQUIS® (apixaban)	enoxaparin/warfarin	RR (95% CI)
Overall	59/2609	71/2635	0.84 (0.60, 1.18)
Index event			
PE (with or without DVT)	21/900	23/886	0.90 (0.50, 1.61)
DVT only	38/1698	47/1736	0.83 (0.54, 1.26)
Level of renal impairment			
CrCl ≤50 mL/min	7/169	7/158	0.92 (0.34, 2.53)
CrCl >50 to ≤80 mL/min	14/531	12/530	1.17 (0.55, 2.50)
CrCl >80 mL/min	38/1676	42/1719	0.93 (0.60, 1.43)



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.

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).[3]

SELECTED IMPORTANT SAFETY INFORMATION: WARNINGS AND PRECAUTIONS (cont'd)

- Spinal/Epidural Anesthesia or Puncture: Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

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

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

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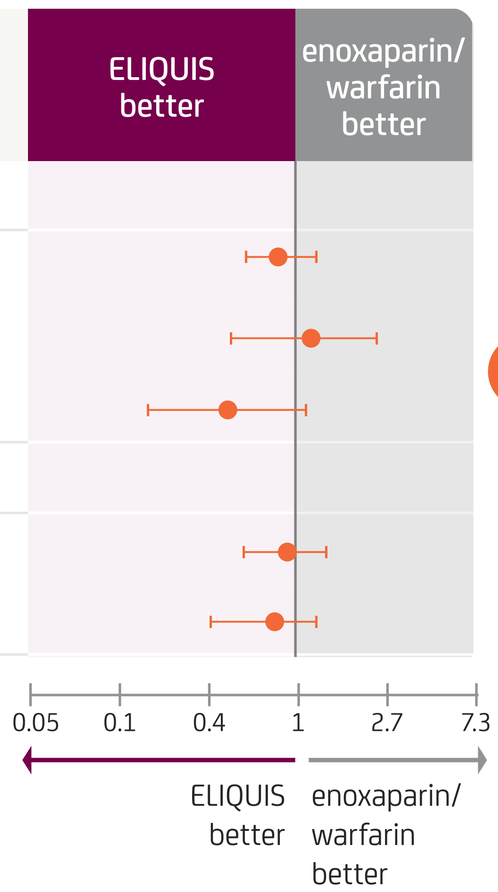
EFFICACY

For the treatment of DVT/PE,

Rates of VTE*/VTE-related death across key patient subgroups[1-3]

n of events/N of patients

	ELIQUIS® (apixaban)	enoxaparin/warfarin	RR (95% CI)
Age			
<65 years	39/1678	47/1714	0.85 (0.56, 1.29)
65 to <75 years	13/542	11/561	1.19 (0.54, 2.63)
≥75 years	7/389	13/360	0.50 (0.20, 1.24)
Sex			
Male	35/1524	38/1557	0.94 (0.60, 1.48)
Female	24/1085	33/1078	0.72 (0.43, 1.21)



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*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).[3]

SELECTED IMPORTANT SAFETY INFORMATION: WARNINGS AND PRECAUTIONS (cont'd)

- Spinal/Epidural Anesthesia or Puncture: Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

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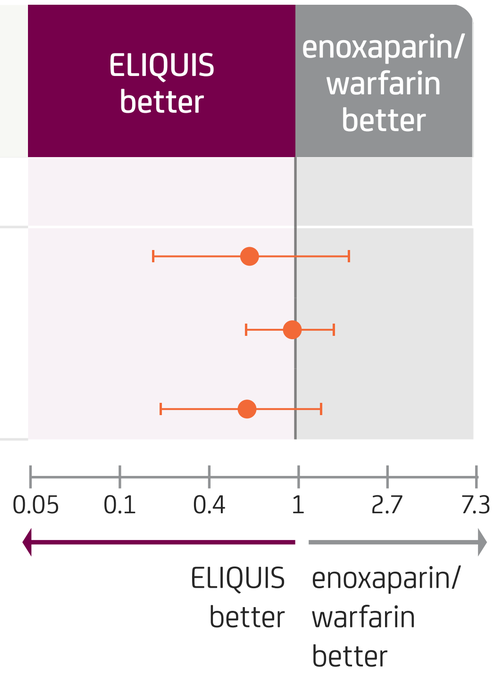
EFFICACY

For the treatment of DVT/PE,

Rates of VTE*/VTE-related death across key patient subgroups[1-3]

n of events/N of patients

	ELIQUIS® (apixaban)	enoxaparin/warfarin	RR (95% CI)
Weight			
≤60 kg	6/225	10/232	0.63 (0.23, 1.72)
>60 kg to <100 kg	42/1870	43/1892	0.99 (0.65, 1.50)
≥100 kg	11/509	18/508	0.61 (0.29, 1.28)



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*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).[3]

SELECTED IMPORTANT SAFETY INFORMATION: WARNINGS AND PRECAUTIONS (cont'd)

- Spinal/Epidural Anesthesia or Puncture: Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

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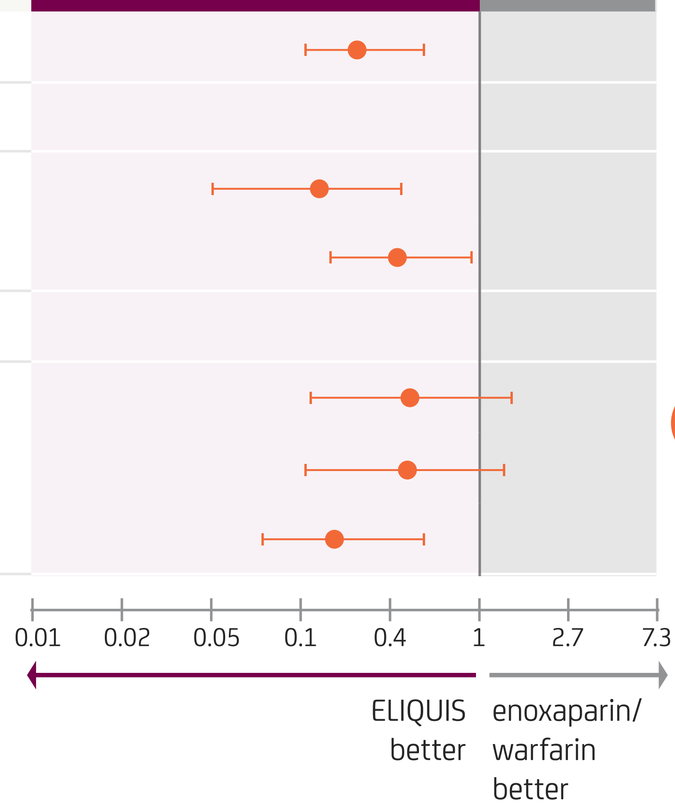
SAFETY

For the treatment of DVT/PE,

Rates of major bleeding across key patient subgroups[1-3]

n of events/N of patients

	ELIQUIS® (apixaban)	enoxaparin/warfarin	RR (95% CI)
Overall	15/2676	49/2689	0.31 (0.17, 0.55)
Index event			
PE (with or without DVT)	4/928	25/902	0.16 (0.05, 0.45)
DVT only	11/1738	24/1773	0.47 (0.23, 0.95)
Level of renal impairment			
CrCl ≤50 mL/min	5/175	9/163	0.53 (0.18, 1.62)
CrCl >50 to ≤80 mL/min	5/549	10/544	0.50 (0.17, 1.44)
CrCl >80 mL/min	5/1720	25/1756	0.20 (0.08, 0.53)



ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

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.

References: 1. Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808. **2.** Data on file: APIX 090. Bristol-Myers Squibb Company, Princeton, NJ. **3.** ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY.

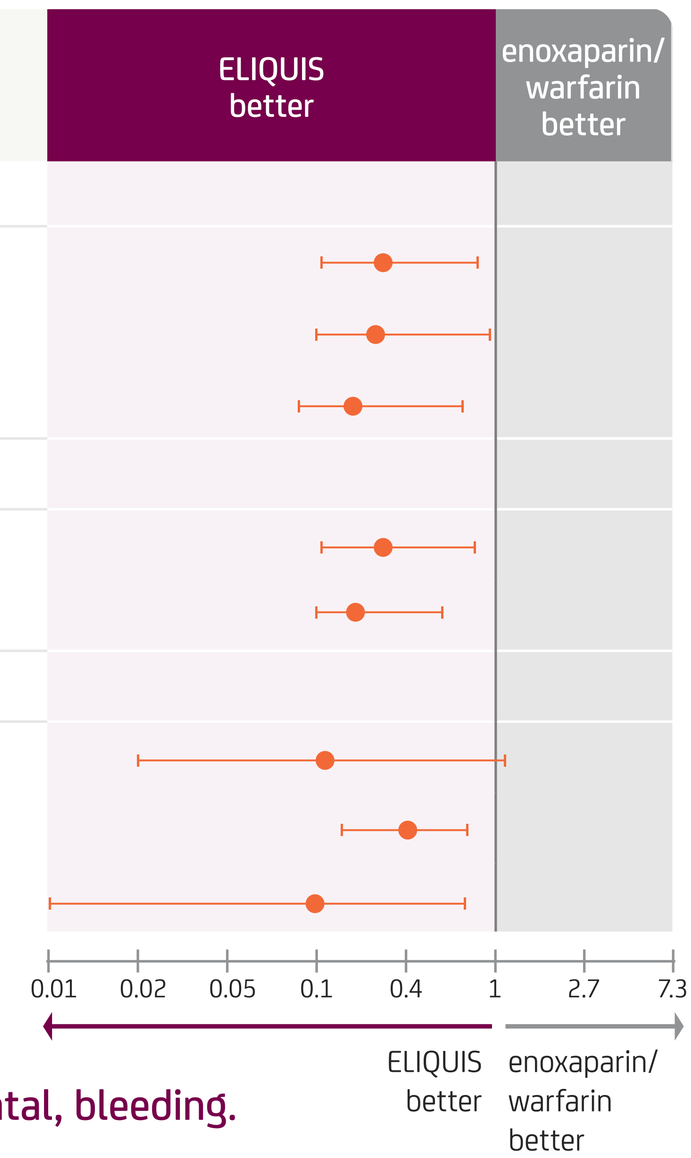
SAFETY

For the treatment of DVT/PE,

Rates of major bleeding across key patient subgroups[1-3]

n of events/N of patients

	ELIQUIS® (apixaban)	enoxaparin/warfarin	RR (95% CI)
Age			
<65 years	7/1725	20/1753	0.36 (0.15, 0.84)
65 to <75 years	4/553	13/566	0.32 (0.10, 0.98)
≥75 years	4/398	16/370	0.23 (0.08, 0.69)
Sex			
Male	9/1561	24/1591	0.38 (0.18, 0.82)
Female	6/1115	25/1098	0.23 (0.10, 0.56)
Weight			
≤60 kg	1/230	7/243	0.15 (0.02, 1.15)
>60 kg to <100 kg	13/1920	32/1924	0.41 (0.21, 0.77)
≥100 kg	1/521	10/518	0.10 (0.01, 0.78)



ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

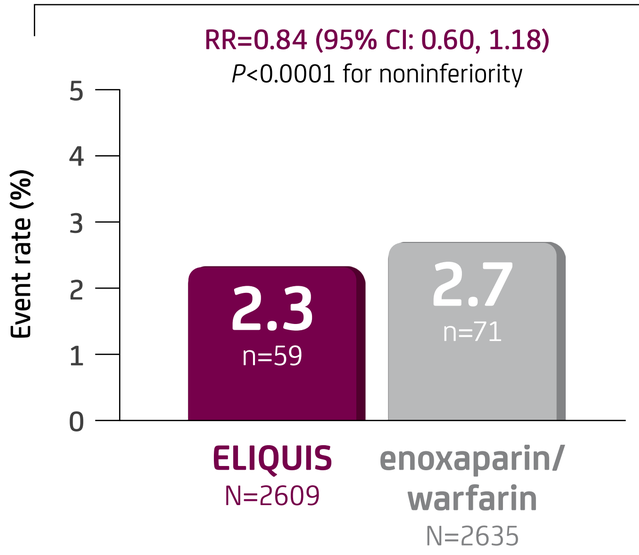
Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular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

References: 1. Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808. **2.** Data on file: APIX 090. Bristol-Myers Squibb Company, Princeton, NJ. **3.** ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY.

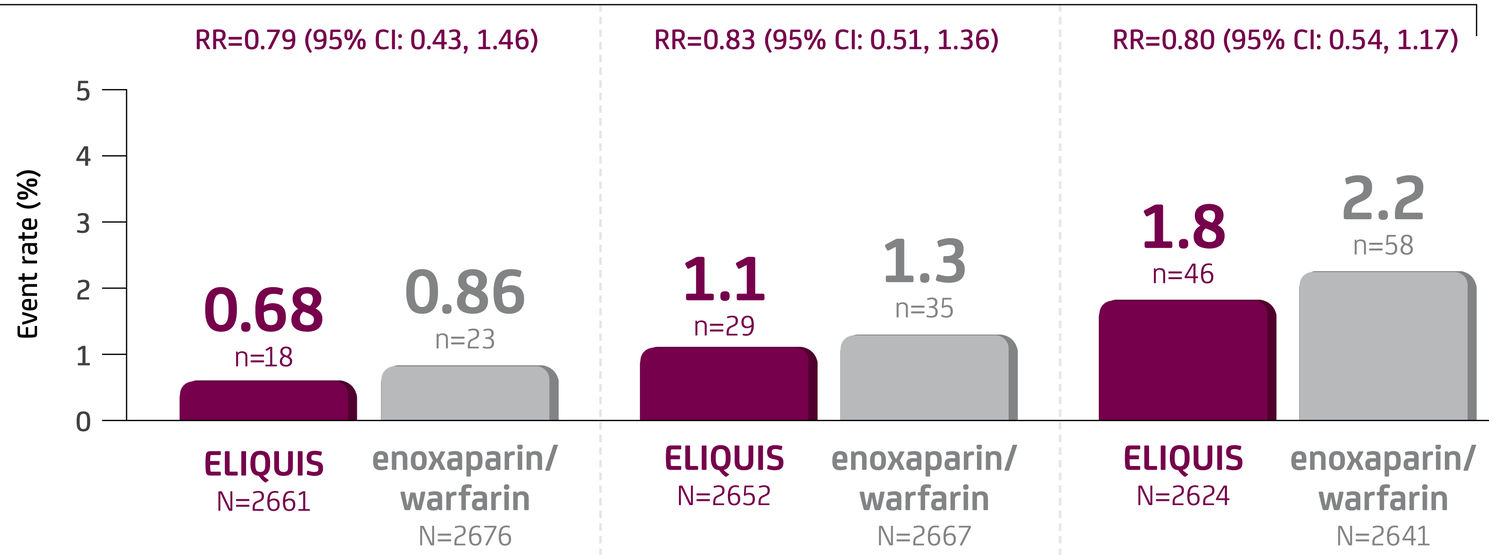
AMPLIFY primary efficacy analysis and post-hoc analysis of select early time points[1,2]

RELATIVE RISKS FOR EFFICACY FOR SELECT EARLY TIME POINTS IN THE AMPLIFY POST-HOC ANALYSIS WERE CONSISTENT WITH THE AMPLIFY PRIMARY EFFICACY ANALYSIS

AMPLIFY primary efficacy analysis[1]
In VTE*/VTE-related death



AMPLIFY time point analysis (post hoc) efficacy data at 7, 21, and 90 days[2]
In VTE*/VTE-related death



Limitations of AMPLIFY time point analysis

- Time point analysis was not predefined in AMPLIFY protocol[2]
- For Days 7 and 21, a small number of events were observed within the short time period, which contributed to less power to assess treatment effect[2]

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).

SELECTED IMPORTANT SAFETY INFORMATION: WARNINGS AND PRECAUTIONS (cont'd)

- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Raskob GE, Gallus AS, Sanders P, et al. Early time courses of recurrent thromboembolism and bleeding during apixaban or enoxaparin/warfarin therapy. A sub-analysis of the AMPLIFY trial. *Thromb Haemost*. 2016;115(4):809-816.

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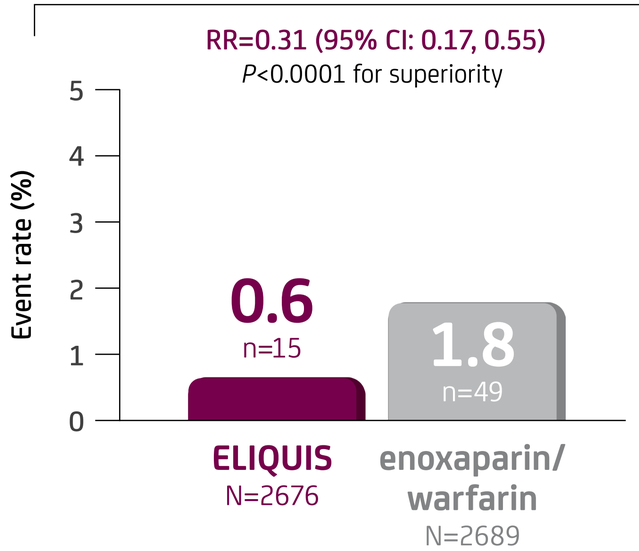
AMPLIFY primary major bleeding analysis and post-hoc analysis of select early time points[1,2]

RELATIVE RISK FOR MAJOR BLEEDING FOR SELECT EARLY TIME POINTS IN THE AMPLIFY POST-HOC ANALYSIS WERE CONSISTENT WITH THE AMPLIFY PRIMARY SAFETY ANALYSIS

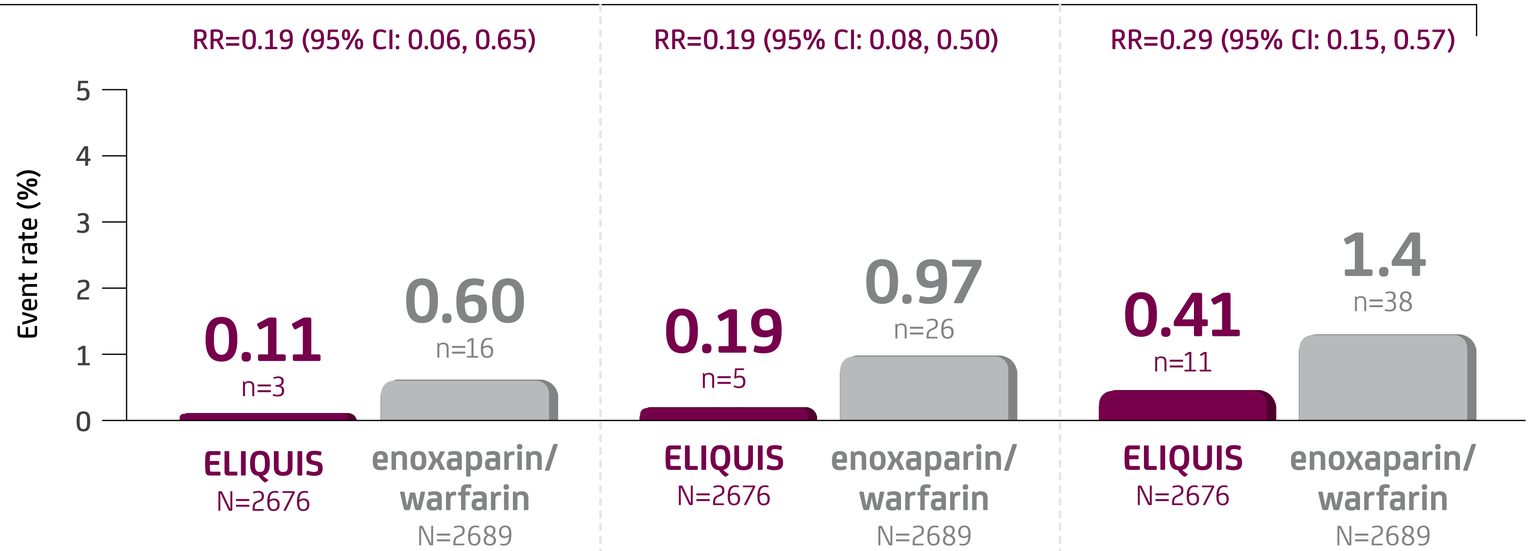
AMPLIFY primary safety analysis[1]

Major bleeding*



AMPLIFY time point analysis (post hoc) safety data at 7, 21, and 90 days[2]

Major bleeding*



Limitations of AMPLIFY time point analysis

- Time point analysis was not predefined in AMPLIFY protocol[2]
- For Days 7 and 21, a small number of events were observed within the short time period, which contributed to less power to assess treatment effect[2]

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

- In AMPLIFY, discontinuation rate due to bleeding events: 0.7% in patients treated with ELIQUIS vs 1.7% in patients treated with enoxaparin/warfarin
- In AMPLIFY, the most commonly observed adverse reactions in patients treated with ELIQUIS (incidence ≥1%) were epistaxis, contusion, hematuria, menorrhagia, hematoma, hemoptysis, rectal hemorrhage, and gingival bleeding

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

SELECTED IMPORTANT SAFETY INFORMATION: WARNINGS AND PRECAUTIONS (cont'd)

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

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Raskob GE, Gallus AS, Sanders P, et al. Early time courses of recurrent thromboembolism and bleeding during apixaban or enoxaparin/warfarin therapy. A sub-analysis of the AMPLIFY trial. *Thromb Haemost*. 2016;115(4):809-816.

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AMPLIFY-EXT: a randomized, double-blind, phase 3 trial for the reduction in the risk of recurrent deep vein thrombosis (DVT)/pulmonary embolism (PE) following initial therapy[1,2]

INDICATION

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

SELECTED IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

Continue

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Agnelli G, et al. *N Engl J Med.* 2013;368(8):699-708.

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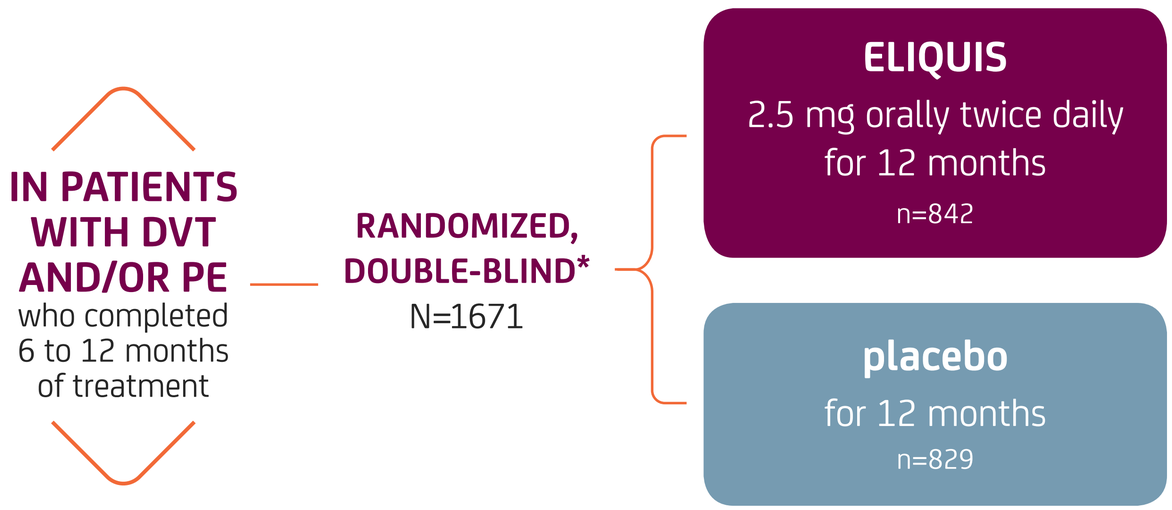
AMPLIFY-EXT was a randomized, double-blind, phase 3 trial[1,2]

Primary objective:

To compare the efficacy and safety of ELIQUIS vs placebo in patients who had been treated for objectively confirmed, symptomatic DVT or PE (with or without DVT) for 6 to 12 months with anticoagulation therapy without having a recurrent event, and for whom HCPs were uncertain about continuing anticoagulation therapy



Primary efficacy endpoint: recurrent DVT or PE† or all-cause death
Primary safety endpoint: major bleeding

Baseline characteristics:

- Patients had either an unprovoked DVT or PE at baseline (approximately 92%) or a provoked baseline event and one additional risk factor for recurrence (approximately 8%)[2]
- Approximately one-third of patients participated in the AMPLIFY study prior to enrollment in AMPLIFY-EXT[1]

Major bleeding was defined as clinically overt bleeding accompanied by ≥1 of the following[2-4]: a decrease in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal; and fatal bleeding.

Select inclusion criteria: objectively confirmed, symptomatic proximal DVT and/or PE.

Select exclusion criteria: multiple episodes of unprovoked DVT or PE.

HCP=health care provider.
*In AMPLIFY-EXT, 2486 patients were randomized, with 815 of these patients randomized to ELIQUIS 5 mg twice daily, which is not an approved dose for this indication.
†Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).

SELECTED IMPORTANT SAFETY INFORMATION: DRUG INTERACTIONS

- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors.
  Clarithromycin
  Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699-708. **3.** Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699-708. **4.** Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost*. 2015;13(12):2187-2191.

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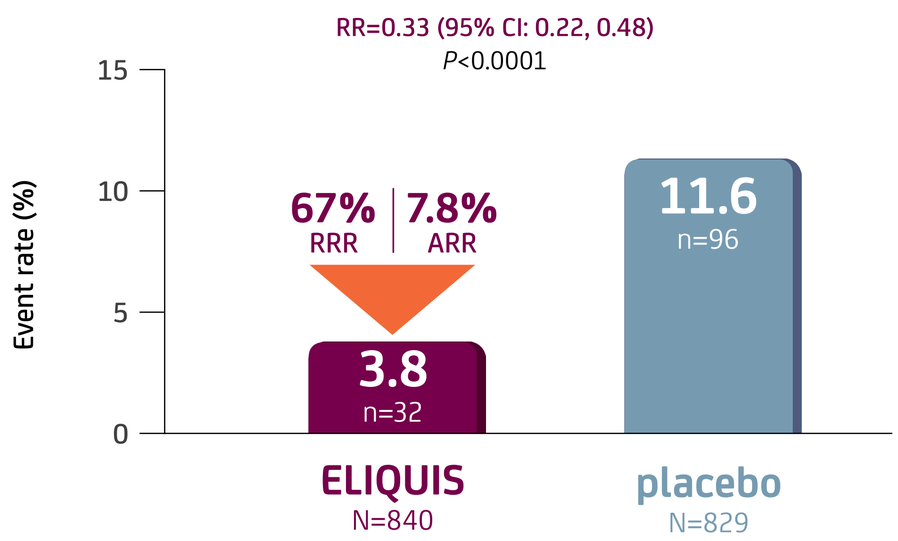
For reducing the risk of recurrent DVT/PE following initial therapy,

ELIQUIS demonstrated superior efficacy AND a similar rate of major bleeding events vs placebo[1,2]

SUPERIOR

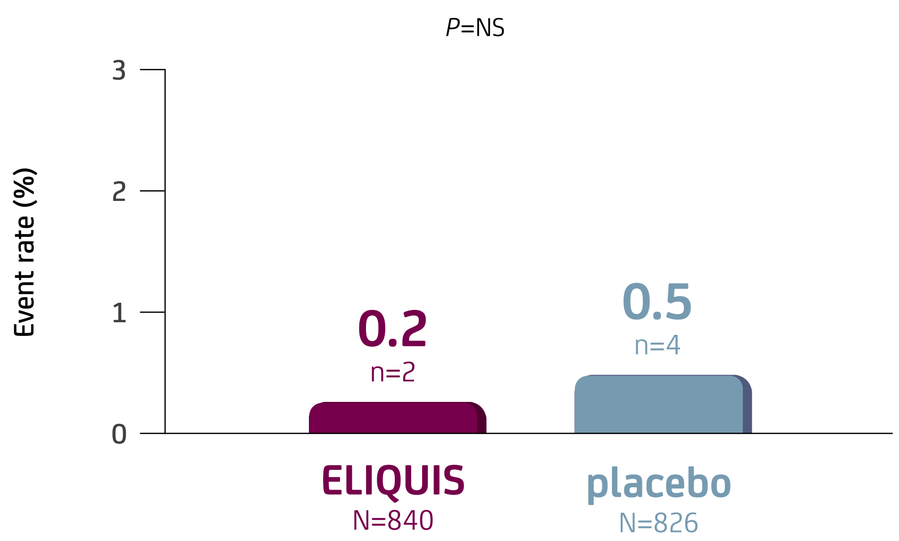
Recurrent VTE*/all-cause death



Primary efficacy endpoint

SIMILAR TO PLACEBO

Major bleeding†



Primary safety endpoint

Why placebo?

The placebo arm simulated patients with DVT/PE who would have received no further treatment after completing initial therapy.

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

- Discontinuation rate due to bleeding events: 1.0% with ELIQUIS vs 0.4% with placebo
- In AMPLIFY-EXT, the most commonly observed adverse reactions in patients treated with ELIQUIS (incidence ≥1%) were epistaxis, hematuria, hematoma, contusion, and gingival bleeding

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).
†Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

SELECTED IMPORTANT SAFETY INFORMATION: DRUG INTERACTIONS (cont'd)

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

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699-708.

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From selected double-blind, randomized, phase 3 trials

Summary of primary efficacy and safety endpoints[1-3]

		PROVEN EFFICACY Primary **efficacy** endpoint	MAJOR BLEEDING EVENTS Primary **safety** endpoint
For the treatment of VTE	**AMPLIFY** **ELIQUIS** vs enoxaparin/ warfarin	**COMPARABLE** **IN VTE*/VTE-RELATED DEATH** 2.3% (59/2609) with ELIQUIS vs 2.7% (71/2635) with enoxaparin/warfarin RR=0.84 (95% CI: 0.60, 1.18) *P*<0.0001 for noninferiority 16% RRR, 0.4% ARR	**SUPERIOR** **IN MAJOR BLEEDING EVENTS†** 0.6% (15/2676) with ELIQUIS vs 1.8% (49/2689) with enoxaparin/warfarin RR=0.31 (95% CI: 0.17, 0.55) *P*<0.0001 69% RRR, 1.2% ARR
For reducing the risk of recurrent DVT/ PE following initial therapy	**AMPLIFY-EXT** **ELIQUIS** vs placebo	**SUPERIOR** **IN RECURRENT VTE*/ ALL-CAUSE DEATH** 3.8% (32/840) with ELIQUIS 2.5 mg twice daily vs 11.6% (96/829) with placebo RR=0.33 (95% CI: 0.22, 0.48) *P*<0.0001 67% RRR, 7.8% ARR	**SIMILAR TO PLACEBO** **IN MAJOR BLEEDING EVENTS†** 0.2% (2/840) with ELIQUIS 2.5 mg twice daily vs 0.5% (4/826) with placebo *P*=NS

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

- In AMPLIFY, the discontinuation rate due to bleeding events was 0.7% in patients treated with ELIQUIS compared with 1.7% in patients treated with enoxaparin/warfarin
- In AMPLIFY, the most commonly observed adverse reactions in patients treated with ELIQUIS (incidence ≥1%) were epistaxis, contusion, hematuria, menorrhagia, hematoma, hemoptysis, rectal hemorrhage, and gingival bleeding
- In AMPLIFY-EXT, the discontinuation rate due to bleeding events was approximately 1.0% with ELIQUIS vs 0.4% with placebo
- In AMPLIFY-EXT, the most commonly observed adverse reactions in patients treated with ELIQUIS (incidence ≥1%) were epistaxis, hematuria, hematoma, contusion, and gingival bleeding

Major bleeding was defined as clinically overt bleeding accompanied by ≥1 of the following[3-5]: a decrease in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal; and fatal bleeding.

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).
†Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

SELECTED IMPORTANT SAFETY INFORMATION: DRUG INTERACTIONS (cont'd)

- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

References: 1. ELIQUIS® (apixaban). Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc., New York, NY. **2.** Connolly SJ, Eikelboom J, Joyner C, et al; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. N *Engl J Med.* 2011;364(9):806-817. **3.** Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368(8):699-708. **4.** Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808. **5.** Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost*. 2015;13(12):2187-2191.

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IMPORTANT SAFETY INFORMATION

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

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

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

- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of ELIQUIS and neuraxial procedures is not known

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

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

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

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

(continued on next page)

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Prosthetic Heart Valves: The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy: Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.
- Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome (APS): Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive APS. For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

DRUG INTERACTIONS

- Combined P-gp and Strong CYP3A4 Inhibitors: Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors.
  Clarithromycin
  Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.
- Combined P-gp and Strong CYP3A4 Inducers: Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.
- Anticoagulants and Antiplatelet Agents: Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY

- The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery, and in the fetus and neonate.
  - *Labor or delivery*: ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches.

(continued on next page)

IMPORTANT SAFETY INFORMATION (cont'd)

LACTATION

- Breastfeeding is not recommended during treatment with ELIQUIS.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

- Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician. The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including ELIQUIS should be assessed in these patients and those with abnormal uterine bleeding.

Please see **Important Safety Information** throughout and **Full Prescribing Information**, including **Boxed WARNINGS**, or visit **ELIQUIS.com**.

Eliquis® (apixaban) tablets 5mg 2.5mg