

# U.S. FDA Approves Eliquis (apixaban) for the Treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), and for the Reduction in the Risk of Recurrent DVT and PE Following Initial Therapy

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Eliquis demonstrated noninferiority in the primary efficacy endpoint of recurrent symptomatic venous thromboembolism (VTE) or VTE-related death versus enoxaparin/warfarin in the AMPLIFY trial. Eliquis demonstrated superiority in the primary safety endpoint of major bleeding versus enoxaparin/warfarin in the AMPLIFY trial.

[Bristol-Myers Squibb Company](#) (NYSE: BMY) and [Pfizer Inc.](#) (NYSE: PFE) today announced the U.S. Food and Drug Administration (FDA) has approved a Supplemental New Drug Application (sNDA) for *Eliquis* for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. Combined, DVT and PE are known as VTE. It is estimated that every year, approximately 900,000 Americans are affected by DVT and PE.

“We are pleased that *Eliquis* is now available as an effective treatment option for DVT and PE,” said Douglas Manion, M.D., Head of Specialty Development, Bristol-Myers Squibb. “*Eliquis* offers oral dosing, no routine coagulation testing, and does not require the use of a parenteral anticoagulant or bridging during initiation.”

“DVT, which may lead to PE, can be a serious medical condition, with PE requiring immediate medical attention for treatment. Once a VTE has occurred, approximately 33 percent of patients are at risk of a recurrence within 10 years,” said Steve Romano, senior vice president, Head of Medicines Development Group for Global Innovative Pharmaceuticals, Pfizer Inc. “The Bristol-Myers Squibb and Pfizer alliance is committed to delivering important treatment options to patients and physicians.”

The full Prescribing Information for *Eliquis* includes Boxed Warnings for the increased risk of thrombotic events in patients who prematurely discontinue *Eliquis*; and for the increased risk of epidural or spinal hematoma, which may cause long-term or permanent paralysis, in patients using *Eliquis* and undergoing spinal epidural anesthesia or spinal puncture.

*Eliquis* increases the risk of bleeding and can cause serious, potentially fatal, bleeding. Please see the complete Boxed Warnings and additional Important Safety Information in this press release.

The FDA approval of *Eliquis* for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy, is based on data from the global AMPLIFY and AMPLIFY-EXT studies.

The AMPLIFY study, a randomized, double-blind trial, was designed to demonstrate the efficacy and safety of *Eliquis* for the treatment of DVT and PE, and included patients with confirmed symptomatic DVT or PE (2,609 for *Eliquis* and 2,635 for standard of care, which was initial enoxaparin treatment for at least five days, overlapped by warfarin therapy [International Normalized Ratio (INR) range 2.0-3.0] orally for six months).

In the AMPLIFY study, *Eliquis* 10 mg twice daily for one week followed by 5 mg twice daily for six months demonstrated efficacy comparable to standard of care in treating DVT and PE patients for the primary efficacy composite endpoint of recurrent, symptomatic VTE, or VTE-related death (2.3% vs. 2.7%, relative risk, 0.84; 95% confidence interval [CI], 0.60 to 1.18; P-value<0.0001 for noninferiority).

*Eliquis* demonstrated superiority in the primary safety endpoint of major bleeding versus standard of care (0.6% vs. 1.8%, relative risk 0.31; 95% CI, 0.17 to 0.55; P<0.0001 for superiority). Major bleeding was defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in the hemoglobin level of 2 g/dL or more; a transfusion of two or more 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, retroperitoneal; or bleeding that was fatal.

For the secondary safety endpoint in the AMPLIFY study, the event rates for clinically relevant nonmajor bleeding (CRNM) were fewer in *Eliquis*-treated patients compared to standard of care-treated patients (3.9% vs. 8.0%). CRNM was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with a medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment in carrying out daily activities.

In AMPLIFY, the discontinuation rate due to bleeding events was 0.7% in the *Eliquis*-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients.

## **About DVT and PE**

DVT is a blood clot in a vein, usually in the lower leg, thigh, or pelvis, which partially or totally blocks the flow of blood. PE is a blood clot blocking one or more vessels in the lungs. DVT causes multiple symptoms including pain, swelling, and redness, and more importantly, can progress to PE, which carries the risk of sudden death.

## **About *Eliquis***

*Eliquis* (apixaban) is an oral selective Factor Xa inhibitor. By inhibiting Factor Xa, a key blood-clotting protein, *Eliquis* decreases thrombin generation and blood clot formation. *Eliquis* is approved for multiple indications in the U.S. based on efficacy and safety data, including results from seven Phase 3 clinical trials.

## **ELIQUIS Important Safety Information**

### **Indications**

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

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

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

### Important Safety Information

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

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

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

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

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

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

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **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 anti-platelet 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.
- There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with Eliquis undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

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

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

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

## ADVERSE REACTIONS

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

## TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

## DRUG INTERACTIONS

- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses greater than 2.5 mg twice daily, the dose of ELIQUIS should be decreased by 50% when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or

clarithromycin). For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp.

- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.
- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

## **PREGNANCY CATEGORY B**

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

**Please see full Prescribing Information, including BOXED WARNINGS and Medication Guide, available at [www.bms.com](http://www.bms.com).**

## **About the Bristol-Myers Squibb/Pfizer Collaboration**

In 2007, Pfizer and Bristol-Myers Squibb entered into a worldwide collaboration to develop and commercialize apixaban, an oral anticoagulant discovered by Bristol-Myers Squibb. This global alliance combines Bristol-Myers Squibb's long-standing strengths in cardiovascular drug development and commercialization with Pfizer's global scale and expertise in this field.

## **About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit [www.bms.com](http://www.bms.com).

## **About Pfizer Inc.: Working together for a healthier world™**

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, Pfizer has worked to make a difference for all who rely on us. To learn more, please

visit us at [www.pfizer.com](http://www.pfizer.com).

## **Bristol-Myers Squibb Forward-Looking Statement**

*This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding product development. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that the approval of these additional indications in the U.S. will lead to increased commercial success or that Eliquis will be approved for any other additional indications. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2013, in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.*

### **PFIZER DISCLOSURE NOTICE:**

*The information contained in this release is as of August 21, 2014. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.*

*This release contains forward-looking information about Eliquis's (apixaban's) potential benefits and about additional indications for Eliquis in the U.S. for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties regarding the commercial success of the additional indications in the U.S.; whether and when regulatory authorities in other jurisdictions will approve applications for these potential additional indications, as well as their decisions regarding labeling and other matters that could affect the availability or commercial potential of such potential additional indications; and competitive developments.*

*A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2013 and in our subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the SEC and available at [www.sec.gov](http://www.sec.gov) and [www.pfizer.com](http://www.pfizer.com).*

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