



# UPDATE: With Multimedia: U.S. FDA Approves ELIQUIS® (apixaban) to Reduce the Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

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ELIQUIS Demonstrated Superior Risk Reductions Versus Warfarin in Three Key Outcomes—Stroke and Systemic Embolism, Major Bleeding and All-Cause Mortality—for Patients with Nonvalvular Atrial Fibrillation

"The approval of ELIQUIS offers patients with nonvalvular atrial fibrillation a novel treatment option for reducing the risk of stroke,"

(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) and Pfizer Inc. (NYSE: PFE) announced that the U.S. Food and Drug Administration (FDA) approved ELIQUIS® (apixaban) to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Atrial fibrillation, the most common type of irregular heartbeat, affects approximately 5.8 million people in the U.S., and results in a five times greater risk of stroke. In the U.S., 15 percent of strokes are attributable to atrial fibrillation.

"The approval of ELIQUIS offers patients with nonvalvular atrial fibrillation a novel treatment option for reducing the risk of stroke," said Lamberto Andreotti, chief executive officer, Bristol-Myers Squibb. "ELIQUIS is the result of leading scientific innovation and the shared vision of our alliance to introduce a new oral anticoagulant for patients with nonvalvular atrial fibrillation in the U.S."

Ian Read, chairman and chief executive officer, Pfizer Inc. said, "The profile of ELIQUIS, combined with the strong legacy and complementary capabilities that Pfizer and Bristol-Myers Squibb have in the cardiovascular space, positions us well to deliver this important new treatment option to patients and health care professionals."

The ELIQUIS clinical trial program is the largest completed clinical development program designed to evaluate risk reduction of stroke or systemic embolism in nonvalvular atrial fibrillation patients; it included two landmark Phase 3 studies -- ARISTOTLE and AVERROES -- in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. ARISTOTLE evaluated ELIQUIS versus warfarin in 18,201 patients with nonvalvular atrial fibrillation who were suitable for warfarin therapy, and AVERROES evaluated ELIQUIS versus aspirin in 5,598 patients with nonvalvular atrial fibrillation who were considered unsuitable for treatment with warfarin.

The Full Prescribing Information for ELIQUIS includes a Boxed Warning for patients who discontinue treatment. Patients on ELIQUIS who discontinue treatment are at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal bleeding. Please see additional Important Safety Information included in this release.

"With a population that is living longer, the prevalence of nonvalvular atrial fibrillation is increasing, but many patients are still not being managed effectively with warfarin," said Christopher Granger, M.D., Professor of Medicine, Duke Clinical Research Institute, Duke University Medical Center, Durham, N.C., ARISTOTLE lead investigator. "ELIQUIS represents a significant advance over warfarin for health care professionals to reduce the risk of stroke in patients with nonvalvular atrial fibrillation."

ELIQUIS is an oral Factor Xa inhibitor anticoagulant. By inhibiting Factor Xa, a key blood clotting protein, ELIQUIS decreases thrombin generation and blood clot formation. ELIQUIS does not require routine monitoring using International Normalized Ratio (INR) or other tests of coagulation and there are no known dietary restrictions. ELIQUIS can be taken with or without food.

ELIQUIS is expected to be widely available in the U.S. by the end of January 2013.

Efficacy and Safety Profile of ELIQUIS in Patients with Nonvalvular Atrial Fibrillation

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) study was designed to compare the effects of ELIQUIS and warfarin on the risk of stroke and systemic embolism. In ARISTOTLE, 18,201 patients were randomized (9,120 patients to ELIQUIS and 9,081 to warfarin) and were followed for a median of 1.7 years. ARISTOTLE was a double-blind, multi-national trial in patients with nonvalvular atrial fibrillation, and one or more of the following additional risk factors for stroke: prior stroke or transient ischemic attack, prior systemic embolism, age  $\geq 75$  years, arterial hypertension requiring treatment, diabetes mellitus, heart failure  $\geq$  New York Heart Association Class 2, or left ventricular ejection fraction  $\leq 40\%$ . Patients received treatment with ELIQUIS 5 mg orally twice daily (or 2.5 mg twice daily in patients with at least 2 of the following characteristics: age  $\geq 80$  years, body weight  $\leq 60$  kg, or serum creatinine  $\geq 1.5$  mg/dL) or warfarin (target INR range 2.0-3.0).

ELIQUIS is the only oral anticoagulant to demonstrate superior risk reductions versus warfarin in three key outcomes—stroke and systemic embolism, major bleeding, and all-cause mortality—for patients with nonvalvular atrial fibrillation.

In ARISTOTLE, ELIQUIS was superior to warfarin in the primary efficacy endpoint of stroke or systemic embolism, with a 21% relative risk reduction beyond warfarin (1.27%/year versus 1.60%/year, HR=0.79,  $p=0.01$ ). Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic stroke that converted to hemorrhagic stroke. Purely ischemic strokes occurred with similar rates on both drugs.

ELIQUIS was superior to warfarin for the primary safety endpoint of major bleeding, with a 31% relative risk reduction (2.13%/year versus 3.09%/year, HR=0.69,  $p<0.0001$ ). Major bleeding was defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in hemoglobin of 2 g/dL or more; a transfusion of 2 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.

The incidence of major gastrointestinal (GI) bleeds was lower with ELIQUIS compared to warfarin (0.83%/year versus 0.93%/year, HR=0.89 [CI=0.70, 1.14]). GI bleed includes upper GI, lower GI, and rectal bleeding. ELIQUIS demonstrated a significant reduction in intracranial hemorrhage versus warfarin with a 59% relative risk reduction (0.33%/year versus 0.82%/year, HR=0.41 [CI=0.30, 0.57]). Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds. The incidence of major intraocular bleeding was numerically higher with ELIQUIS compared to warfarin (0.21%/year versus 0.14%/year, HR=1.42 [CI=0.83, 2.45]). Intraocular bleed is within the corpus of the eye (a conjunctival bleed is not an intraocular bleed). ELIQUIS demonstrated

a significant reduction in fatal bleeds versus warfarin with a 73% relative risk reduction (0.06%/year versus 0.24%/year, HR=0.27 [CI=0.13, 0.53]). Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal extracranial bleeds and fatal hemorrhagic stroke. Eliquis demonstrated a significant reduction in clinically relevant non major bleeding (CRNM) versus warfarin (2.08%/year for ELIQUIS compared to 3.00%/year for warfarin [HR= 0.70, P<0.0001]). CRNM was defined as clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy.

In AVERROES, ELIQUIS was associated with an increase in major bleeding compared to aspirin that was not statistically significant (1.41%/year versus 0.92%/year, HR 1.54, (95% CI, 0.96 to 2.45); P = 0.07).

ELIQUIS was superior to warfarin in the key secondary endpoint of all-cause mortality, with an 11% relative risk reduction (3.5%/year versus 3.9%/year, HR=0.89, p= 0.046), primarily because of a reduction in cardiovascular death, particularly stroke deaths. Non-vascular death rates were similar in the treatment arms.

The most common and most serious adverse reactions observed in the ARISTOTLE and AVERROES clinical trials with ELIQUIS were related to bleeding. The most common reason for treatment discontinuation was for bleeding-related adverse reactions; in ARISTOTLE, this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively. Patients taking ELIQUIS should be carefully observed and counseled on the symptoms and signs of bleeding.

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of ELIQUIS outweigh the potential risks in patients with nonvalvular atrial fibrillation. The ELIQUIS REMS consists of a communication plan to inform healthcare professionals about the increased risk of thrombotic events, including stroke when discontinuing ELIQUIS without an adequate alternative anticoagulant and the importance of following the recommendations in the U.S. Prescribing Information on how to convert patients with nonvalvular atrial fibrillation from ELIQUIS to warfarin or other anticoagulants.

### ELIQUIS Dosage and Administration

The recommended dose of ELIQUIS for most patients is 5 mg taken orally twice daily. In patients with any two of the following characteristics (age  $\geq$ 80 years, body weight  $\leq$ 60 kg, or serum creatinine  $\geq$ 1.5mg/dL), the recommended dose of ELIQUIS is 2.5 mg twice

daily. The dose of ELIQUIS should be decreased to 2.5 mg twice daily when coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp. 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 non-critical in location and easily controlled. For more detailed information on the dosing of ELIQUIS, please refer to Section 2 of the Full Prescribing Information.

#### IMPORTANT SAFETY INFORMATION for ELIQUIS® (apixaban) 2.5 mg and 5 mg tablets

#### WARNING: DISCONTINUING ELIQUIS IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE.

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

#### CONTRAINDICATIONS

Active pathological bleeding Severe hypersensitivity reaction to ELIQUIS (apixaban) (i.e., anaphylactic reactions)

#### WARNINGS AND PRECAUTIONS

**Increased Risk of Stroke with Discontinuation of ELIQUIS:** Discontinuing 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 patients with nonvalvular atrial fibrillation. If ELIQUIS must be discontinued for a reason other than pathological bleeding, 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. Patients should be made aware of signs or symptoms of blood loss and instructed to immediately report 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 about 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available. Because of high plasma protein binding, apixaban is not expected to be dialyzable. Protamine sulfate and vitamin K would not be 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 neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated charcoal reduces absorption of apixaban thereby lowering apixaban plasma concentrations. Prosthetic Heart Valves: The safety and efficacy of ELIQUIS has not been studied in patients with prosthetic heart valves and is not recommended in these patients.

## ADVERSE REACTIONS

The most common and most serious adverse reactions reported with ELIQUIS (apixaban) were related to bleeding.

## DISCONTINUATIONS 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.

## 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. Decrease the dose of ELIQUIS to 2.5 mg twice daily when coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking ELIQUIS at a dose of 2.5 mg daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp. **Strong Dual Inducers of CYP3A4 and P-gp:** Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke. 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. **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the

risk of bleeding.

## 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.

## INDICATION

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

Please see full Prescribing Information including BOXED WARNING 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 ELIQUIS, an investigational 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 <http://www.bms.com> or follow us on Twitter at <http://twitter.com/bmsnews>.

Pfizer Inc.: Working together for a healthier world™

At Pfizer, we apply science and our global resources to improve health and well-being at every stage of life. We strive to set the standard for quality, safety and value in the discovery, development and manufacturing of medicines for people and animals. Our diversified global health care portfolio includes human and animal biologic and small molecule medicines and vaccines; as well as many of the world's best-known consumer 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 the world's leading

biopharmaceutical company, we also 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.

### 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 ELIQUIS will become a commercially successful product. 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, 2011, 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 January 2, 2013. 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 (apixaban) that involves substantial risks and uncertainties. Such risks and uncertainties include, among other things, (i) the uncertainties regarding the commercial success of ELIQUIS in the U.S. for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; (ii) the ability to meet the anticipated timing for the availability of Eliquis in the U.S.; (iii) decisions by regulatory authorities in jurisdictions in which applications are pending or may be filed for ELIQUIS for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation regarding whether and when to approve such applications, as well as their decisions regarding labeling and other matters that could affect the availability or commercial potential of that indication in such jurisdictions; and (iv) 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, 2011 and in its reports on Form 10-Q and Form 8-K.

This press release has an accompanying Smart Marketing Page providing further details about the organization, products and services introduced above. You can access the Smart Marketing Page via the following link:

<http://smp.newshq.businesswire.com/pages/eliquis-apixaban-tablets-now-approved>

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