# Anticoagulant Effect of Eliquis (apixaban) Reversed by Two Separate 4-Factor Prothrombin Complex Concentrates in Healthy Subjects

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Data Presented Today at the 56th Annual American Society of Hematology (ASH) Meeting

Bristol-Myers Squibb Company (NYSE: BMY) and Pfizer Inc. (NYSE: PFE) today announced results of the first human study evaluating the reversal of the anticoagulant effect of *Eliquis* (apixaban) by 4-factor prothrombin complex concentrates (PCCs) in healthy subjects. The study results demonstrated that both PCCs, Sanquin's *Cofact* (a heparin-free formulation) and CSL Behring's *Beriplex P/N* (a formulation containing heparin) reversed the steady-state pharmacodynamic effects of *Eliquis* in several coagulation assessments, including endogenous thrombin potential (ETP). The full data will be presented today during the Antithrombotic Therapy: Anticoagulant Therapy session at the 56th annual meeting of the American Society of Hematology (ASH) in San Francisco, CA.

"The Bristol-Myers Squibb and Pfizer alliance remains committed to delivering important treatment options to patients and physicians and is pleased with the positive results of this study investigating the potential use of these PCCs to reverse the anticoagulant effect of *Eliquis*," said Steven Romano, MD, senior vice president and head, Medicines Development Group, Pfizer Global Innovative Pharmaceutical Business. "These results support further evaluation of the use of PCCs in *Eliquis*-treated subjects."

"Throughout our collaboration with Pfizer, the alliance has been dedicated to further investigating the use and application of *Eliquis*," said Douglas Manion, MD, head of

specialty development, Bristol-Myers Squibb. “We are pleased with the positive results of this study and look forward to further exploration of prothrombin complex concentrates.”

*Eliquis* is a novel oral anticoagulant that specifically inhibits Factor Xa. This study evaluated the effect of two non-activated 4-factor PCCs, *Cofact* and *Beriplex P/N*, on *Eliquis* pharmacodynamics and pharmacokinetics in healthy subjects. *Cofact* and *Beriplex P/N* are used to stop severe bleeding in patients taking vitamin K antagonists, such as warfarin, or with a blood clotting factor deficiency. Currently there are no approved reversal agents for *Eliquis* or other direct Factor Xa inhibitors.

The study was an open label, randomized, placebo-controlled, three-period crossover study in 15 healthy, adult subjects (mean age 33±7 years). Within each period, subjects received *Eliquis* 10 mg twice daily. On day four (after steady-state was achieved), three hours after *Eliquis* administration, subjects received a 30-minute infusion of 4-factor PCCs, either 50 IU/kg *Cofact* or *Beriplex P/N*, or an equivalent volume of saline solution. The effect of *Cofact* and *Beriplex P/N* on the pharmacodynamics of *Eliquis* was based upon changes in endogenous thrombin potential, a measure of thrombin-mediated coagulation. Treatment periods were separated by an 11-day washout, after which the alternate treatment was administered.

The mean *Eliquis* pharmacokinetic profiles were consistent across all treatment groups and were not affected by PCC administration. Following completion of the 30-minute *Cofact* infusion, the effect of *Eliquis* on ETP was significantly reduced compared to placebo ($p < 0.001$). Following completion of the 30-minute *Beriplex P/N* infusion, the effect of *Eliquis* on ETP was reduced; however, this did not achieve statistical significance ($p > 0.05$). Mean ETP was comparable to the day four *Eliquis* pre-dose value (steady-state trough *Eliquis* concentration) at the end of the *Cofact* infusion and 30 minutes after completing the *Beriplex P/N* infusion. Mean ETP was within the baseline value (*Eliquis* naïve) within 5.5 hours after completing the infusion for both PCCs.

In this study, no serious adverse events, bleeding-related events or signs of thrombosis were reported with *Eliquis* administration with or without PCC treatment.

Overall, these data demonstrate that *Cofact* and *Beriplex P/N* reversed the steady-state pharmacodynamic effects of *Eliquis* as measured by ETP and support further evaluation of PCCs in the management of patients treated with *Eliquis* who require reversal of its anticoagulant effect.

**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* is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; 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; for the treatment of DVT and PE; and to reduce the risk of recurrent DVT and PE following initial therapy.

**ELIQUIS Indications and 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.

**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 or follow us on Twitter at http://twitter.com/bmsnews.

**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.

**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. 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 December 8, 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* and 4-factor prothrombin complex concentrates (PCCs), including their potential benefits, 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 inherent in research and development, including the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; whether and when any drug applications may be filed for any PCCs for the reversal of the anticoagulant effect of *Eliquis*; whether and when regulatory authorities will approve any such applications; 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 its 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 and www.pfizer.com.

Bristol-Myers Squibb Media: Danielle Halstrom, 609-419-5512, danielle.halstrom@bms.com Investors: Ranya Dajani, 609-252-5330, ranya.dajani@bms.com Ryan Asay, 609-252-5020, ryan.asay@bms.com Pfizer Inc. Media: Steven Danehy, 212-733-1538, steven.danehy@pfizer.com Andrew Widger, +44-1737-330909, andrew.widger@pfizer.com Investors: Ryan Crowe, 212-733-8160, ryan.crowe@pfizer.com