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U.S. FDA Approves Eliquis® (apixaban) To Reduce The Risk Of Blood Clots Following Hip Or Knee Replacement Surgery

Friday, March 14, 2014 - 09:00am

PRINCETON, N.J. & NEW YORK--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) and Pfizer Inc. (NYSE: PFE) today announced that the U.S. Food and Drug Administration (FDA) approved a Supplemental New Drug Application (sNDA) for *Eliquis* (apixaban) 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.

“Today’s FDA approval of *Eliquis* for DVT prophylaxis in patients who have undergone hip or knee replacement is a significant milestone for this important medicine, which is also approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation,” said Brian Daniels, M.D., senior vice president, global development and medical affairs, Bristol-Myers Squibb. “This approval reflects the continued commitment of the alliance to deliver new treatment options for patients and physicians.”

“As the number of hip and knee replacement surgeries performed in the U.S. continues to increase, the risk of DVT following these surgeries remains a concern for physicians,” said Steven J. Romano, M.D., senior vice president and Medicines Development Group Head, Global Innovative Pharmaceuticals Business, Pfizer Inc. “ *Eliquis* provides patients and physicians with a new treatment option that offers twice daily oral dosing and no routine coagulation testing, and is broadly accessible through hospitals and managed health care formularies.”

The full Prescribing Information for *Eliquis* includes Boxed Warnings for the increased risk of stroke in patients with nonvalvular atrial fibrillation who discontinue *Eliquis* without adequate continuous anticoagulation; 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. Please see complete Boxed Warnings and additional Important Safety Information in this press release.

DVT, a blood clot that forms in a large vein, usually in the lower leg, thigh, or pelvis, can lead to PE when a portion or all of a blood clot breaks off and travels to the lungs, blocking one or more blood vessels. PE can lead to sudden death.

Based on recent data, each year in the U.S. an estimated 719,000 total knee replacement surgeries and 332,000 hip replacement surgeries are performed. Patients undergoing hip or knee replacement surgery without thromboprophylaxis are at risk for developing DVT and PE.Guidelines recommend the use of anticoagulants for the prophylaxis of DVT and PE for most patients undergoing orthopedic surgery.

“DVT, which may lead to PE, is a serious medical condition,” said Richard J. Friedman, M.D., FRCSC, Professor of Orthopaedic Surgery, Medical University of South Carolina. “The FDA approval of *Eliquis* gives U.S. orthopedic surgeons a new option for DVT prophylaxis in both hip and knee replacement surgery.”

This sNDA approval for *Eliquis* is supported by three clinical trials (the ADVANCE clinical trial program). The ADVANCE trials randomized more than 11,000 patients, with 5,770 receiving *Eliquis* and 5,755 receiving enoxaparin, to assess the safety and efficacy of *Eliquis*.

In December 2013, the FDA accepted for review another sNDA for *Eliquis* for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE.

INDICATION

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.

IMPORTANT SAFETY INFORMATION

WARNINGS: (A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA

(A) 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.

(B) When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins, heparinoids, or Factor Xa inhibitors for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Monitor patients for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary. Consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Increased Risk of Stroke with Discontinuation of ELIQUIS in Patients with Nonvalvular Atrial Fibrillation:** 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 at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure. 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 have 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.

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 5 mg twice daily, the dose of ELIQUIS should be decreased when it is 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 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.
- **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.

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 to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery.

About Deep Vein Thrombosis and Pulmonary Embolism

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.

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 *Eliquis*, 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 http://www.bms.com or follow us on Twitter athttp://twitter.com/bmsnews.

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 atwww.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 March 14, 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 (apixaban), including its potential benefits, that involves substantial risks and uncertainties. Such risks and uncertainties include, among other things, (i) uncertainty regarding the commercial success of the indication for Eliquis for the prophylaxis of DVT in patients who have undergone hip or knee replacement surgery; (ii) whether and when ELIQUIS may be approved by the U.S. Food and Drug Administration (FDA) for the treatment of DVT and PE and for the reduction in the risk of recurrent DVT and PE, as well as the FDA's decisions regarding labeling and other matters that could affect the availability or commercial potential of that additional indication for Eliquis; and (iii) 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 reports on Form 10-Q and Form 8-K.

Bristol-Myers Squibb Shelly Mittendorf (Media) 609-252-5799 shelly.mittendorf@bms.com or Ranya Dajani (Investors) 609-252-5330 ranya.dajani@bms.com or Ryan Asay (Investors) 609-252-5020 ryan.asay@bms.com or Pfizer Inc. Jennifer Kokell (Media) 917-741-4254 jennifer.kokell@pfizer.com or Ryan Crowe (Investors) 212-733-8160 ryan.crowe@pfizer.com