



NEWS RELEASE

Findings to be Presented at Annual Scientific Session of the American College of Cardiology (ACC) About an Additional Potential Reversal Strategy for and Real-World Safety Performance of XARELTO®

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- March 15, 2015, 4:15PM PT: Post-Marketing Pharmacovigilance Study for the Active Detection and Evaluation of Major Bleeding in Rivaroxaban Users with Non-Valvular Atrial Fibrillation
- March 16, 2015, 11:30AM PT: ANNEXA™-R: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial, Demonstrating Reversal of Rivaroxaban-Induced Anticoagulation in Older Subjects by Andexanet Alfa (PRT064445), a Universal Antidote for Factor Xa (fXa) Inhibitors

Raritan, NJ (March 2, 2015) - Full results from a Phase 3 study examining Portola Pharmaceutical's developmental compound andexanet alfa found it rapidly and significantly reversed the blood thinning (anticoagulant) effects of XARELTO® (rivaroxaban). These results, from the first part of the ANNEXA™-R (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXa Inhibitors - Rivaroxaban) study, will be presented at the 64th Annual Scientific Session of the American College of Cardiology (ACC) on March 16, 2015. Additional findings to be presented at the meeting include new 24-month results from an ongoing, five-year, observational study of people with non-valvular atrial fibrillation taking XARELTO®, which showed the rates and patterns of major bleeding in routine clinical practice were generally consistent with those observed in Phase 3 clinical trials used to approve the medicine for this indication.

Janssen and its development partner, Bayer HealthCare, previously entered into a second clinical collaboration agreement with Portola to initiate the Phase 3 study to evaluate Portola's investigational Factor Xa inhibitor agent,

andexanet alfa, in reversing the blood thinning effect of XARELTO[®], should the need arise. This clinical collaboration will be in effect through completion of the Phase 3 study with XARELTO[®] and any potential U.S. and EU regulatory approval of andexanet alfa. The second part of the Phase 3 ANNEXA-R study, evaluating a continuous infusion of andexanet alfa, is ongoing.

Specifically, this first part of the ANNEXA-R study found andexanet alfa, when administered as an intravenous bolus dose, significantly reversed the anti-clotting effect of XARELTO[®]. In the randomized, double-blind, placebo-controlled study, a total of 41 healthy adults age 50 to 75 were given XARELTO[®] 20 mg once daily for four days to steady state. On day four, participants were randomized in a 2:1 ratio to receive either an 800 mg intravenous dose of andexanet alfa or placebo. Efficacy was evaluated using biomarker endpoints, with anti-Factor Xa levels as the primary endpoint. Secondary endpoints included plasma levels of unbound XARELTO[®] and thrombin generation levels. All primary and secondary endpoints were met with statistical significance ($p < 0.0001$). Andexanet alfa was well tolerated with no serious or severe adverse events reported.

These findings add to existing published research examining reversal measures for blood thinners:

- Prior research on potential reversal options for XARELTO[®] include a Phase 2 study published in the Journal of Thrombosis and Haemostasis, which showed prothrombin complex concentrate, or PCC, partially reversed the blood thinning effect of XARELTO[®] in healthy people. In the study, 35 adults were treated with 20 mg of XARELTO[®] twice daily for four days. On the fifth day, an intravenous dose of PCC (either three-factor or four-factor) or a single control dose of saline was given. The PCCs (both three-factor and four-factor) were found to partially reverse the anti-clotting effect of XARELTO[®].
- Vitamin K, a common reversal option for patients taking warfarin, can take up to 24 hours to reverse the anticoagulant effect of warfarin. Notably, stopping treatment with XARELTO[®] may allow for patients to return to near-normal levels of coagulation within 24 hours.

"Patients taking blood thinners are doing so to treat or help prevent life-threatening blood clots from forming in their body. If the need arises to stop this effect, andexanet alfa may add to current reversal strategies for XARELTO[®]," said Paul Burton, M.D., Ph.D., Vice President, Medical Affairs, Janssen. "Stopping treatment with XARELTO[®] may allow for patients to return to near-normal levels of coagulation within 24 hours. In addition, the use of prothrombin complex concentrate, or PCC, has been observed to partially reverse the anticoagulant or blood thinning activity of XARELTO[®] in healthy people."

Real-World Safety Data Also to be Presented at ACC

At ACC on March 15, 2015, Janssen will also present new, confirmatory, real-world safety data of people with non-valvular atrial fibrillation (NVAf) taking XARELTO[®]. Specifically, 24-month results from an ongoing, five-year, observational study of people with NVAf found the rates and patterns of major bleeding in routine clinical practice

were generally consistent with those observed in Phase 3 clinical trials used to approve XARELTO® for this indication.

"We are pleased with these findings that reaffirm the safety profile of XARELTO®," said Dr. Burton. "With studies completed in over 85,000 patients and ongoing post-marketing studies that will include more than 74,000 patients, we continue to provide real-world data to equip doctors with the information that they need to optimize care for people taking XARELTO®."

In this study, researchers reviewed health records of people with NVAf using once-daily XARELTO®. Of the 39,052 people taking XARELTO®, 970 experienced a major bleeding event, which translated into an incidence rate of 2.89 per 100 person-years. Incidence rate was calculated using a person-time approach: the total number of people experiencing major bleeding divided by the number of years of all people receiving XARELTO® (expressed in 100-year increments).

About XARELTO® (rivaroxaban)

XARELTO® works by blocking the blood clotting Factor Xa. XARELTO® does not require routine blood monitoring. XARELTO® has a broad indication profile and is approved for six indications that include:

To reduce the risk of strokes and blood clots in patients with atrial fibrillation not caused by a heart valve problem. For patients currently well managed on warfarin, there is limited information on how XARELTO® and warfarin compare in reducing the risk of stroke.

To treat patients with deep vein thrombosis (DVT).

To treat patients with pulmonary embolism (PE).

To reduce the risk of recurrence of DVT or PE following an initial six-month treatment for acute venous thromboembolism.

To reduce the risk of blood clots in the legs and lungs of patients who have just had knee replacement surgery.

To reduce the risk of blood clots in the legs and lungs of patients who have just had hip replacement surgery.

IMPORTANT SAFETY INFORMATION:

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT XARELTO®?

- For people taking XARELTO® for atrial fibrillation:

People with atrial fibrillation (an irregular heart beat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. XARELTO® lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking XARELTO®, you may have increased risk of forming a clot in your blood.

Do not stop taking XARELTO[®] without talking to the doctor who prescribes it for you. Stopping XARELTO[®] increases your risk of having a stroke.

If you have to stop taking XARELTO[®], your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.

- XARELTO[®] can cause bleeding, which can be serious, and rarely may lead to death. This is because XARELTO[®] is a blood thinner medicine that reduces blood clotting. While you take XARELTO[®] you are likely to bruise more easily and it may take longer for bleeding to stop.

You may have a higher risk of bleeding if you take XARELTO[®] and take other medicines that increase your risk of bleeding, including:

- Aspirin or aspirin-containing products
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Warfarin sodium (Coumadin[®], Jantoven[®])
- Any medicine that contains heparin
- Clopidogrel (Plavix[®])
- Other medicines to prevent or treat blood clots

Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

Call your doctor or get medical help right away if you develop any of these signs or symptoms of bleeding:

- Unexpected bleeding or bleeding that lasts a long time, such as:
 - Nosebleeds that happen often
 - Unusual bleeding from gums
 - Menstrual bleeding that is heavier than normal, or vaginal bleeding
- Bleeding that is severe or that you cannot control
- Red, pink, or brown urine
- Bright red or black stools (looks like tar)
- Cough up blood or blood clots
- Vomit blood or your vomit looks like "coffee grounds"
- Headaches, feeling dizzy or weak

- Pain, swelling, or new drainage at wound sites

Spinal or epidural blood clots (hematoma): People who take a blood thinner medicine (anticoagulant) like XARELTO[®], and have medicine injected into their spinal and epidural area, or have a spinal puncture, have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:

- A thin tube called an epidural catheter is placed in your back to give you certain medicine
- You take NSAIDs or a medicine to prevent blood from clotting
- You have a history of difficult or repeated epidural or spinal punctures
- You have a history of problems with your spine or have had surgery on your spine

If you take XARELTO[®] and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots. Tell your doctor right away if you have back pain, tingling, numbness, muscle weakness (especially in your legs and feet), or loss of control of the bowels or bladder (incontinence).

XARELTO[®] is not for patients with artificial heart valves.

WHO SHOULD NOT TAKE XARELTO[®]?

Do not take XARELTO[®] if you:

- Currently have certain types of abnormal bleeding. Talk to your doctor before taking XARELTO[®] if you currently have unusual bleeding.
- Are allergic to rivaroxaban or any of the ingredients of XARELTO[®].

WHAT SHOULD I TELL MY DOCTOR BEFORE OR WHILE TAKING XARELTO[®]?

Before taking XARELTO[®], tell your doctor if you:

- Have ever had bleeding problems
- Have liver or kidney problems
- Have any other medical condition
- Are pregnant or plan to become pregnant. It is not known if XARELTO[®] will harm your unborn baby. Tell your doctor right away if you become pregnant while taking XARELTO[®]. If you take XARELTO[®] during pregnancy, tell your doctor right away if you have bleeding or symptoms of blood loss.
- Are breastfeeding or plan to breastfeed. It is not known if XARELTO[®] passes into your breast milk. You and your doctor should decide if you will take XARELTO[®] or breastfeed.

Tell all of your doctors and dentists that you are taking XARELTO[®]. They should talk to the doctor who

prescribed XARELTO® for you before you have any surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way XARELTO® works. Certain medicines may increase your risk of bleeding. See "What is the most important information I should know about XARELTO®?"

Especially tell your doctor if you take:

- Ketoconazole (Nizoral®)
- Itraconazole (Onmel™, Sporanox®)
- Ritonavir (Norvir®)
- Lopinavir/ritonavir (Kaletra®)
- Indinavir (Crixivan®)
- Carbamazepine (Carbatrol®, Equetro®, Tegretol®, Tegretol®-XR, Teril™, Epitol®)
- Phenytoin (Dilantin-125®, Dilantin®)
- Phenobarbital (Solfoton™)
- Rifampin (Rifater®, Rifamate®, Rimactane®, Rifadin®)
- St. John's wort (Hypericum perforatum)

Ask your doctor if you are not sure if your medicine is one listed above. Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

HOW SHOULD I TAKE XARELTO®?

Take XARELTO® exactly as prescribed by your doctor.

Do not change your dose or stop taking XARELTO® unless your doctor tells you to.

- Your doctor will tell you how much XARELTO® to take and when to take it.
- Your doctor may change your dose if needed.

If you take XARELTO® for:

WHAT ARE THE POSSIBLE SIDE EFFECTS OF XARELTO®?

Please see "What is the most important information I should know about XARELTO®?" above.

Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You are also encouraged to report side effects to the FDA: visit <http://www.fda.gov/medwatch> or call 1-800-FDA-1088. You may also report side effects to Janssen Pharmaceuticals, Inc., at 1-800-JANSSEN (1-800-526-7736).

Please click **here** for full Prescribing Information, including Boxed Warnings, and Medication Guide. 011417-140307

Janssen and Bayer HealthCare together are developing rivaroxaban. Portola Pharmaceuticals, Inc. is developing andexanet alfa.

For more information about XARELTO[®], visit www.xarelto-us.com. The XARELTO[®] CarePath[™] Support Program is a resource designed for healthcare providers, patients and caregivers. Visit www.xareltocarepath.com or call 1-888-XARELTO to learn more about the XARELTO[®] CarePath[™] resources focused on access, education and adherence.

About Janssen

At Janssen, we are dedicated to addressing and solving some of the most important unmet medical needs of our time in oncology, immunology, neuroscience, infectious diseases and vaccines, and cardiovascular and metabolic diseases. Driven by our commitment to patients, we develop innovative products, services and healthcare solutions to help people throughout the world. Janssen Pharmaceuticals, Inc. is one of the Janssen Pharmaceutical Companies of Johnson & Johnson. Please visit JanssenPharmaceuticalsInc.com for more information.

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