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**Phase 3b Study Shows Significantly Less Bleeding with XARELTO® (rivaroxaban) Compared to Warfarin in People with Non-Valvular Atrial Fibrillation Following Percutaneous Coronary Intervention with Stenting**

*Late-Breaking PIONEER AF-PCI Data is Simultaneously Published in The New England Journal of Medicine and is the First to Evaluate a NOAC in this Area of Critical Unmet Need*

*Supporting Sub-Analysis on Re-Hospitalizations Also Simultaneously Published in Circulation*

**NEW ORLEANS, LA (November 14, 2016)** – New Phase 3b results from the PIONEER AF-PCI study met its primary endpoint and showed that both XARELTO® (rivaroxaban) groups had significantly reduced risk of bleeding compared to the warfarin arm in people with non-valvular atrial fibrillation (NVAF) receiving antiplatelet therapy following angioplasty with stenting. The findings of this exploratory, open-label, randomized study were announced today by Janssen Pharmaceuticals, Inc. during a Late-Breaking Clinical Trial session at the American Heart Association (AHA) Scientific Sessions 2016 and simultaneously published in *The New England Journal of Medicine*. A sub-analysis, also published today in *Circulation*, showed people in both XARELTO® groups had a significantly reduced risk of being re-hospitalized compared to those in the warfarin arm.

Among people undergoing percutaneous coronary intervention (PCI), also known as angioplasty, a procedure to open clogged heart arteries, five to eight percent have concomitant NVAF<sup>i,ii,iii</sup>.

Management of people with NVAF following PCI with stenting is challenging, as the risks of NVAF-

related stroke, stent-related blood clots (thrombosis) and bleeding from both oral anticoagulant and antiplatelet therapy must be considered. For people with NVAF following PCI, guidelines recommend "triple therapy", which is a combination of dual antiplatelet therapy (clopidogrel or another thienopyridine plus aspirin) and anticoagulation therapy with a vitamin K antagonist (warfarin), but this regimen comes with recognized increased rates of major bleeding, including intracranial bleeding.

"For the first time in this population, a treatment regimen resulted in less bleeding than the current standard of care," said lead investigator C. Michael Gibson, MS, MD, Professor of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA. "Pairing rivaroxaban with single or dual antiplatelet therapy has the potential to transform current practice as demonstrated in this study with significantly less bleeding and numerically similar efficacy when compared to warfarin with dual antiplatelet therapy."

In PIONEER AF-PCI, researchers examined the safety of XARELTO® compared to warfarin in 2,124 people with NVAF who received background antiplatelet therapy following PCI with stenting. The primary endpoint was clinically significant bleeding (composite of TIMI major bleeding, TIMI minor bleeding or bleeding requiring medical attention). Secondary endpoints included the incidence of the components of TIMI clinically significant bleeding, the composite of major adverse cardiovascular events (cardiovascular death, heart attack or stroke), individual components of the adverse cardiovascular event endpoint and stent-related thrombosis.

"Janssen is continuing to uncover the full potential of the safety and efficacy of XARELTO® in areas of critical medical need," said Paul Burton, MD, PhD, FACC, Vice President, Medical Affairs, Janssen. "PIONEER AF-PCI is an example of that commitment as it is the first study to evaluate a non-vitamin K antagonist oral anticoagulant (NOAC) in people with NVAF following PCI."

Patients were randomized in a 1:1:1 ratio, with one group receiving XARELTO® 15 mg once daily plus single antiplatelet therapy (clopidogrel or another thienopyridine) for 12 months, another group receiving XARELTO® 2.5 mg twice daily with dual antiplatelet therapy (clopidogrel or another thienopyridine plus aspirin), and a third receiving standard "triple therapy," warfarin with dual antiplatelet therapy. Prior to randomization, the duration of dual antiplatelet therapy (one, six or 12 months) was pre-specified for the two relevant groups and the intended thienopyridine (clopidogrel, prasugrel or ticagrelor). At one year:

- Both XARELTO® groups had significantly lower rates of bleeding compared to the group taking warfarin. Specifically, the XARELTO® 15 mg group reduced clinically significant bleeding by 41

percent (Hazard Ratio [HR]=0.59; 95% CI, 0.47 to 0.76;  $p<0.001$ ; absolute rate 16.8 percent), and the XARELTO® 2.5 mg group by 37 percent (HR=0.63; 95% CI, 0.50 to 0.80;  $p<0.001$ ; absolute rate 18 percent) compared to the warfarin group (absolute rate 26.7 percent).

- This reduction in bleeding for the two XARELTO® groups was consistent across multiple subgroups; fatal bleeds were rare and numerically fewer in patients taking XARELTO® compared to those taking warfarin.
- Although the study was not powered to make conclusions on efficacy, both XARELTO® groups showed similar rates of major adverse cardiovascular events compared to the group taking warfarin. Specifically, 6.5 percent of people in the XARELTO® 15 mg group and 5.6 percent in the XARELTO® 2.5 mg group experienced a major adverse cardiovascular event compared to 6.0 percent in the warfarin group.

### **XARELTO® Also Led to Fewer Re-Hospitalizations**

A separate sub-analysis of PIONEER AF-PCI showed a reduction in the risk of re-hospitalization or all-cause mortality (due to an adverse event, including bleeding, a cardiovascular cause or other cause) in both XARELTO® groups compared to the warfarin group. Specifically, all-cause mortality or re-hospitalization was observed in 34.9 percent of the XARELTO® 15 mg group ( $p=0.008$ ) and 31.9 percent of the XARELTO® 2.5 mg group ( $p=0.002$ ) compared to 41.9 percent of the warfarin group. When looking specifically at re-hospitalization, both XARELTO® groups had significantly fewer re-hospitalizations, with 34.1 percent of the XARELTO® 15 mg group ( $p=0.005$ ) and 31.2 percent of the XARELTO® 2.5 mg group ( $p=0.001$ ) being re-hospitalized due to an adverse event compared to 41.5 percent of the warfarin group.

“The costs associated with re-hospitalizations following PCI due to adverse events are substantial and can be burdensome to healthcare delivery systems,” said Dr. Burton. “Results from the PIONEER AF-PCI sub-analysis provide important insights into ways to reduce this cost burden associated with readmissions.”

### **About PIONEER AF-PCI and EXPLORER**

Part of the EXPLORER research program for XARELTO®, PIONEER AF-PCI is a global, exploratory, randomized, multicenter, Phase 3b clinical study assessing the safety of three treatment strategies in a broad group of people from 26 countries with NVAf who had undergone PCI with stenting.

Unmatched by any oral anticoagulant in the NOAC class in its size, scope and ambition, EXPLORER continues to generate important clinical evidence on the safety and efficacy performance of XARELTO®

and its potential role in addressing additional critical medical needs. By the time of its completion, more than 275,000 patients will have participated in EXPLORER, which includes ongoing and completed studies, independent registries and non-interventional studies. The EXPLORER program is a collaborative research effort with Bayer and includes six additional indication-seeking programs underway beyond the currently approved six indications in the U.S.

### **Broad Patient Access**

XARELTO® leads the NOAC class by having the strongest affordability and access position in the U.S. For qualifying people with commercial insurance using the Janssen CarePath savings card, XARELTO® has no cost.<sup>1</sup> XARELTO® is broadly reimbursed, with more than 95 percent of commercial patients and people on Medicare Part D covered at the lowest branded co-pay. The medication is also now preferred by CVS Caremark and has the lowest average out-of-pocket cost of any NOAC available in the U.S. today with more than 25 million prescriptions written for XARELTO® in the U.S. since its launch.

### **WHAT IS XARELTO®?**

XARELTO® is a prescription medicine used to reduce the risk of stroke and blood clots in people 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.

XARELTO® is also a prescription medicine used to treat deep vein thrombosis and pulmonary embolism, and to help reduce the risk of these conditions occurring again.

XARELTO® is also a prescription medicine used to reduce the risk of forming a blood clot in the legs and lungs of people who have just had knee or 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.

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<sup>1</sup> Subject to a maximum annual program benefit of \$3,400.

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®)
- Selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
- 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<sup>®</sup>, 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<sup>®</sup> will harm your unborn baby. Tell your doctor right away if you become pregnant while taking XARELTO<sup>®</sup>. If you take XARELTO<sup>®</sup> 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<sup>®</sup> passes into your breast milk. You and your doctor should decide if you will take XARELTO<sup>®</sup> or breastfeed.

Tell all of your doctors and dentists that you are taking XARELTO<sup>®</sup>. They should talk to the doctor who prescribed XARELTO<sup>®</sup> 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<sup>®</sup> works. Certain medicines may increase your risk of bleeding. **See “What is the most important information I should know about XARELTO<sup>®</sup>?”**

Especially tell your doctor if you take:

- Ketoconazole (Nizoral<sup>®</sup>)
- Itraconazole (Onmel<sup>™</sup>, Sporanox<sup>®</sup>)
- Ritonavir (Norvir<sup>®</sup>)
- Lopinavir/ritonavir (Kaletra<sup>®</sup>)
- Indinavir (Crixivan<sup>®</sup>)
- Carbamazepine (Carbatrol<sup>®</sup>, Equetro<sup>®</sup>, Tegretol<sup>®</sup>, Tegretol<sup>®</sup>-XR, Teril<sup>™</sup>, Eptol<sup>®</sup>)
- Phenytoin (Dilantin-125<sup>®</sup>, Dilantin<sup>®</sup>)
- Phenobarbital (Solfoton<sup>™</sup>)
- Rifampin (Rifater<sup>®</sup>, Rifamate<sup>®</sup>, Rimactane<sup>®</sup>, Rifadin<sup>®</sup>)
- 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<sup>®</sup>?**

Take XARELTO<sup>®</sup> exactly as prescribed by your doctor.

**Do not change your dose or stop taking XARELTO<sup>®</sup> unless your doctor tells you to.**

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

If you take XARELTO<sup>®</sup> for:

- **Atrial Fibrillation:** Take XARELTO<sup>®</sup> 1 time a day with your evening meal. If you miss a dose of XARELTO<sup>®</sup>, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
- **Blood clots in the veins of your legs or lungs:**
  - Take XARELTO<sup>®</sup> once or twice a day as prescribed by your doctor.
  - Take XARELTO<sup>®</sup> with food at the same time each day.
  - If you miss a dose of XARELTO<sup>®</sup>:

- **and take XARELTO® 2 times a day:** Take XARELTO® as soon as you remember on the same day. You may take 2 doses at the same time to make up for the missed dose. Take your next dose at your regularly scheduled time.
  - **and take XARELTO® 1 time a day:** Take XARELTO® as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
  - **Hip or knee replacement surgery:** Take XARELTO® 1 time a day with or without food. If you miss a dose of XARELTO®, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
- If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take XARELTO®.
  - Your doctor will decide how long you should take XARELTO®. Do not stop taking XARELTO® without talking to your doctor first.
  - Your doctor may stop XARELTO® for a short time before any surgery, medical or dental procedure. Your doctor will tell you when to start taking XARELTO® again after your surgery or procedure.
  - Do not run out of XARELTO®. Refill your prescription for XARELTO® before you run out. When leaving the hospital following a hip or knee replacement, be sure that you have XARELTO® available to avoid missing any doses.
  - If you take too much XARELTO®, go to the nearest hospital emergency room or call your doctor right away.

## **WHAT ARE THE POSSIBLE SIDE EFFECTS OF XARELTO®?**

*Please see “What is the most important information I should know about XARELTO®?”*

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.**

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Janssen and Bayer together are developing rivaroxaban.

For more information about XARELTO®, visit [www.xarelto.com](http://www.xarelto.com).

## **About the Janssen Pharmaceutical Companies**

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science. We

are Janssen. We collaborate with the world for the health of everyone in it. Learn more at [www.janssen.com](http://www.janssen.com). Follow us on Twitter at [@JanssenUS](https://twitter.com/JanssenUS).

#### *Cautions Concerning Forward-Looking Statements*

*This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding product development, including the potential of rivaroxaban, and expectations for clinical research programs. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Pharmaceuticals, Inc. or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges inherent in product research and development, including uncertainty of clinical success and obtaining regulatory approvals; competition, including technological advances, new products and patents attained by competitors; challenges to patents; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and description of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 3, 2016, including in Exhibit 99 thereto, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at [www.sec.gov](http://www.sec.gov), [www.jnj.com](http://www.jnj.com) or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies or Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.*

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<sup>i</sup> Rubboli A et al. Periprocedural and medium-term antithrombotic strategies in patients with an indication for long-term anticoagulation undergoing coronary angiography and intervention. *Coronary Artery Disease* 2007; 18(3): 193-199.

<sup>ii</sup> Wang TY et al. Discharge antithrombotic strategies among patients with acute coronary syndrome previously on warfarin anticoagulation: physician practice in the CRUSADE registry. *American Heart Journal* 2008; 155(2): 361-368.

<sup>iii</sup> Pérez-Gómez F et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *Journal of the American College of Cardiology* 2004; 44(8): 1557-1566.