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XARELTO® (rivaroxaban) Significantly Reduced Ischemic Stroke in Patients with Nonvalvular Atrial Fibrillation in Large, Real-World Meta-Analysis of Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)

Since its approval, more than 200,000 people have been evaluated in published real-world research for XARELTO® across all approved indications in the U.S.

TITUSVILLE, NJ, March 11, 2019 — The Janssen Pharmaceutical Companies of Johnson & Johnson today announced new results from a large, real-world meta-analysis of 95 studies investigating the use of non-vitamin K antagonist oral anticoagulants (NOACs), including XARELTO® (rivaroxaban), versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). Results show XARELTO® significantly lowered the risk of ischemic stroke and intracranial hemorrhage (ICH) compared to warfarin. XARELTO® was also the only NOAC to show significantly reduced nonpersistence rates compared to warfarin, meaning that patients were significantly less likely to have a gap in therapy of 60 days. The bleeding profile for each NOAC was consistent with the bleeding profile demonstrated in each respective clinical phase 3 program. Results are now published in the *Journal of Market Access & Health Policy*.[i]

Click to Tweet: Large real-world meta-analysis of NOACs vs. warfarin shows Janssen's blood thinner significantly reduces ischemic stroke and ICH in #AFib patients https://ctt.ec/bE6cd+

"Real-world evidence provides valuable information to help inform treatment decisions for patients, including those with nonvalvular atrial fibrillation," said Craig Coleman[1], PharmD, Professor of Pharmacy Practice, University of Connecticut. "Our findings show that certain NOACs, like rivaroxaban, are performing exceptionally well, and that physicians should feel confident prescribing them to prevent strokes that can often result in irreversible harm and even death."

Anticoagulants, like NOACs and warfarin, are prescribed to people with NVAF to reduce their risk of stroke. In the 2019 update of the AHA/ACC/HRS Guidelines for the Management of Patients with Atrial Fibrillation, NOACs, including XARELTO®, are now recommended over warfarin for stroke prevention.

For the meta-analysis, in addition to observing a significant reduction in ischemic stroke and ICH with XARELTO®, researchers also found that XARELTO® significantly reduced the risk of two composite outcomes: the composite of ischemic stroke and systemic embolism (SE) and the composite of ischemic stroke, SE and all-cause mortality. There was no difference in heart attack, venous thromboembolism (VTE), hemorrhagic stroke (HS) or major bleeding between XARELTO® and warfarin; however, XARELTO® was associated with a higher risk of gastrointestinal (GI) bleeding.

Researchers also evaluated dabigatran and observed a lower risk of ischemic stroke, all-cause mortality, VTE, HS and ICH compared to warfarin, but saw no difference in heart attack, nonpersistence or the two composite efficacy outcomes. Dabigatran was associated with a lower risk of major and any bleeding compared to warfarin; however, it was associated with an increase in GI bleeding.

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[1] Dr. Craig Coleman has received grants and consulting fees from Janssen and Bayer in the last 12 months. He was not compensated for his contributions to this announcement.

Finally, researchers compared apixaban to warfarin and found no difference in ischemic stroke or the composite of ischemic stroke and SE between the two groups. Apixaban was associated with significantly lower rates of ICH, HS, major and GI bleeding and similar rates of any bleeding and nonpersistence compared to warfarin. Researchers also observed a significantly lower risk of the composite of ischemic stroke, SE and all-cause mortality with apixaban.

"This meta-analysis is complementary to what we've seen in clinical trials and what we continue to see in the real world about the positive efficacy and safety profile of XARELTO® across a broad spectrum of patients with NVAF," said Paul Burton, MD, PhD, FACC, Vice President, Medical Affairs, Internal Medicine, Janssen Scientific Affairs, LLC. "We look forward to sharing additional studies like this that demonstrate how XARELTO® is performing in everyday clinical practice."

About the meta-analysis

The meta-analysis was funded by Bayer, Janssen's development partner for XARELTO®. Participants were adults (aged ≥ 18 years) with NVAF. Efficacy outcomes included: ischemic stroke; all-cause mortality; heart attack; VTE; a composite of ischemic stroke or SE; and a composite of ischemic stroke, SE and all-cause mortality. Safety outcomes included: hemorrhagic stroke; ICH; major bleeding; GI bleeding; and any bleeding. In addition, persistence/nonpersistence, defined as a break in treatment of at least 60 days, was the final outcome of interest that was evaluated.

Systematic searches were performed through December 2016 to identify non-randomized NVAF studies comparing NOACs with warfarin, and reporting on effectiveness, safety or persistence. Of the 562 citations identified from Medline, Embase and the Cochrane Library,[ii] 49, 79 and 18 compared XARELTO®, dabigatran and apixaban, respectively, with warfarin and were included in the meta-analysis (some studies involved more than one NOAC). Two independent reviewers performed the study selection with any differences resolved by a third reviewer. If

more than one study used the same database, only the study with the highest level of precision was used; this avoided the same patients being repeatedly included in the meta-analysis to minimize bias.

Real-world data have the potential to supplement randomized controlled trial data by providing additional information about how a medicine performs in routine medical practice; however, they have limitations and cannot be used as stand-alone evidence to validate the efficacy and/or safety of a treatment. Real-world studies are generally far more heterogeneous than randomized clinical trials, with substantial differences among the studies in terms of populations, study designs, outcome definitions, and other features.

More on NVAF

Atrial fibrillation significantly increases a person's risk of ischemic stroke.[iii] In fact, one in three people with NVAF will experience a stroke at some point during their life.[iv] Stroke also is a leading cause of serious long-term disability.[iii]

WHAT IS XARELTO®?

XARELTO® is a prescription medicine used to:

- reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation that is not caused by a heart valve problem. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to the formation of blood clots, which can travel to the brain, causing a stroke, or to other parts of the body
- treat blood clots in the veins of your legs (deep vein thrombosis or DVT) or lungs (pulmonary embolism or PE)
- reduce the risk of blood clots happening again in people who continue to be at risk for DVT or PE after receiving treatment for blood clots for at least 6 months
- help prevent a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery

XARELTO® is also used with low dose aspirin to:

- reduce the reduce the risk of serious heart problems, heart attack and stroke in patients with coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) or peripheral arterial disease (a condition where the blood flow to the legs is reduced)

It is not known if XARELTO® is safe and effective in children.

IMPORTANT SAFETY INFORMATION

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

XARELTO® may cause serious side effects, including:

- **Increased risk of blood clots if you stop taking XARELTO®**.
  People with atrial fibrillation (an irregular heart beat) that is not caused by a heart valve problem (nonvalvular) 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.
- **Increased risk of bleeding.** XARELTO® can cause bleeding which can be serious, and may lead to death. This is because XARELTO® is a blood thinner medicine (anticoagulant) that lowers blood clotting. During treatment with 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
  - Long-term (chronic) use of 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 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 people with artificial heart valves.**

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®.

Before taking XARELTO®, tell your doctor about all your medical conditions, including if you:
- Have ever had bleeding problems
- Have liver or kidney problems
- 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 during treatment with XARELTO®. Taking XARELTO® while you are pregnant may increase the risk of bleeding in you or in your unborn baby.
  - If you take XARELTO® during pregnancy, tell your doctor right away if you have any signs or symptoms of bleeding or blood loss. **See "What is the most important information I should know about XARELTO®?" for signs and symptoms of bleeding.**

- Are breastfeeding or plan to breastfeed. XARELTO® may pass 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 over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way XARELTO® works, causing side effects. Certain medicines may increase your risk of bleeding. **See "What is the most important information I should know about XARELTO®?"**

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 may change your dose if needed.
- If you take XARELTO® for:
  - **Atrial Fibrillation that is not caused by a heart valve problem:**
    - Take XARELTO® **1 time a day with your evening meal**.
    - 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.
  - **Blood clots in the veins of your legs or lungs:**
    - Take XARELTO® **1 or 2 times a day** as prescribed by your doctor.
    - For the **15-mg and 20-mg doses,** XARELTO® **should be taken with food.**
    - For the **10-mg dose**, XARELTO® **may be taken with or without food.**
    - Take your XARELTO® doses at the same time each day.
    - If you miss a dose:
      - **If you take the 15-mg dose of XARELTO 2 times a day (a total of 30 mg of XARELTO in 1 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.
      - **If you 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.
  - **Reducing the risk of serious heart problems, heart attack and stroke in coronary artery disease or peripheral arterial disease:**
    - Take XARELTO® 2 times a day with or without food.

    - If you miss a dose of XARELTO®, take your next dose at your regularly scheduled time.
- If you have difficulty swallowing the XARELTO® tablet whole, talk to your doctor about other ways to take XARELTO®.
- Your doctor will decide how long you should take XARELTO®**.**
- XARELTO® may need to be stopped, if possible for one or more days before any surgery or medical/dental procedure. If you need to stop taking XARELTO® for any reason, talk to your doctor to find out when you should stop taking it. **Do not stop taking XARELTO® without first talking to the doctor who prescribed it to you.** 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®?

- The most common side effect of XARELTO® was bleeding.
- **See "What is the most important information I should know about XARELTO®?"**

Call your doctor for medical advice about side effects. **You may report side effects to FDA at 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.

 Janssen and Bayer together are developing rivaroxaban. For more information about XARELTO®, visit www.xarelto.com.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal. Janssen Pharmaceuticals, Inc., and Janssen Scientific Affairs, LLC, are two of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding XARELTO® (rivaroxaban). 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., any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; [manufacturing difficulties and delays;] competition, including technological advances, new products and patents attained by competitors; challenges to patents; [product efficacy or safety concerns resulting in product recalls or regulatory action;] changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions 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 December 30, 2018, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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[i] Craig I. Coleman, Jean-Baptiste Briere, Laurent Fauchier, Pierre Levy, Kevin Bowrin, Mondher Toumi, Aurélie Millier, Vanessa Taieb & Olivia Wu (2019) Meta-analysis of real-world evidence comparing non-vitamin K antagonist oral anticoagulants with vitamin K antagonists for the treatment of patients with non-valvular atrial fibrillation, Journal of Market Access & Health Policy, 7:1, 1574541, DOI: 10.1080/20016689.2019.1574541

[ii] Cochrane Library includes the Cochrane Database of Systemic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Registers of Controlled Clinical Trials (CENTRAL), Health Technology Assessment (HTA) database, and the NHS Economic Evaluation Database (NHS EED).

[iii] Atrial fibrillation fact sheet. 2011. at https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm. Accessed March 8, 2019.

[iv] StopAfib.org. Stroke Risks from AFib. http://www.stopafib.org/stroke.cfm. Accessed February 20, 2019.