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XARELTO® (rivaroxaban) Significantly Reduced Major Cardiovascular Events in Patients with Stable Coronary and Peripheral Artery Disease in Pivotal Phase 3 Study

- *XARELTO® vascular dose (2.5 mg twice daily) plus aspirin 100 mg once daily reduced the combined risk of cardiovascular death, stroke and heart attack by 24% compared to aspirin alone*
- *Significantly fewer major amputations and major adverse limb events noted in subgroup analysis of patients with stable peripheral artery disease treated with combination regimen of XARELTO®/aspirin*
- *The risk of major bleeding was significantly higher in patients taking the XARELTO®/aspirin regimen, with no significant increase in fatal or intracranial bleeds*

BARCELONA, SPAIN (August 27, 2017) – Results from the pivotal Phase 3 COMPASS study found that the XARELTO® (rivaroxaban) vascular dose (2.5 mg twice daily) plus aspirin 100 mg once daily significantly reduced the risk of major cardiovascular (CV) events defined as CV death, heart attack or stroke by 24% in patients with stable coronary and/or peripheral artery disease (CAD/PAD) compared to aspirin alone. This finding was driven by a robust 42% reduction in any stroke and 22% reduction in CV death. The risk of major bleeding was significantly higher in patients taking the XARELTO®/aspirin regimen compared to aspirin alone, with no significant increase in fatal or intracranial bleeds. Findings from this global, randomized, superiority study were announced today by Janssen Research & Development, LLC, presented during a Hot Line session at the ESC Congress 2017 and simultaneously published in [The New England Journal of Medicine](#).

[Click to Tweet: Pivotal COMPASS data show lower CV events with blood thinner plus aspirin regimen in stable #PAD #CAD #ESCCongress http://po.st/gbV8rG](http://po.st/gbV8rG)

Both CAD and PAD occur when arteries become hardened or narrowed due to a buildup of cholesterol and plaque, limiting blood flow to parts of the body. CAD occurs in the blood vessels that feed the heart, and PAD occurs in other blood vessels in the body (most often the legs, but also the brain, arms and abdomen). People with CAD might experience symptoms such as shortness of breath and chest pressure, while those with PAD may have painful cramping and numbness or weakness in their legs. A public health burden, CAD and PAD affect 16.5 millionⁱ and 10 million Americansⁱⁱ, respectively, and can lead to serious health issues, like heart attack, stroke and even death.

Despite use of preventative medicines as directed by current guidelines, approximately 5% of people with CAD or PAD will experience a debilitating or fatal CV event each year.ⁱⁱⁱ Part of the EXPLORER clinical research program, COMPASS is the only randomized study to investigate a Factor Xa inhibitor, specifically XARELTO[®], in preventing major CV events in this population.

"The results of COMPASS represent a true breakthrough in CAD and PAD, as they confirm the combination regimen of XARELTO[®] and aspirin is highly effective and well-tolerated in preventing the devastating and irreversible CV events that often occur in these patients," said COMPASS lead investigator Dr. John Eikelboom, Associate Professor, Division of Hematology & Thromboembolism, Department of Medicine, McMaster University, Hamilton Health Sciences, Hamilton, Ontario. "In addition to achieving a positive balance of efficacy and safety, we observed a considerable reduction in stroke and CV death, which could have a profound effect on how physicians manage patients with stable CAD and PAD."

COMPASS, the largest clinical study of XARELTO[®] to date, enrolled a total of 27,395 patients with stable CAD and/or PAD. Patients were randomized in a 1:1:1 ratio, with one group receiving the XARELTO[®] 2.5 mg twice-daily vascular dose plus aspirin 100 mg once daily regimen, another group receiving XARELTO[®] 5 mg twice daily, and the final group receiving aspirin 100 mg once daily. Earlier this year, Janssen and its development partner Bayer announced [COMPASS was being stopped approximately one year ahead of schedule due to efficacy](#), which was based on the recommendation of the study's independent Data Monitoring Committee.

COMPASS met its primary efficacy endpoint, with the XARELTO[®]/aspirin regimen shown to be superior to aspirin alone, reducing major CV events by 24%. Specifically, 4.1% of patients receiving the XARELTO[®]/aspirin regimen experienced a CV event compared to 5.4% of those receiving aspirin alone (HR=0.76; 95% CI, 0.66-0.86; p<0.001).

Researchers also made the following observations:

- Specifically, the XARELTO®/aspirin regimen reduced the risk of any stroke by 42% (HR 0.58; 95% CI, 0.44-0.76; $p < 0.001$), CV death by 22% (HR 0.78; 95% CI, 0.64-0.96; $p = 0.02$) and heart attack by 14% (HR 0.86; 95% CI, 0.70-1.05; $p = 0.14$).
- For composite secondary efficacy outcomes, the XARELTO®/aspirin regimen was superior to aspirin alone. Notably, the XARELTO®/aspirin regimen reduced the combined secondary endpoint of coronary heart disease death, heart attack, ischemic stroke and acute limb ischemia by 28% compared to aspirin alone (3.6% vs. 4.9%; HR=0.72; 95% CI, 0.63-0.83; $p < 0.001$).
- The hazard ratio for all-cause mortality for the XARELTO®/aspirin regimen compared to aspirin alone was 0.82 (95% CI, 0.71-0.96; $p = 0.01$).
- Major bleeding was significantly higher in the XARELTO®/aspirin regimen with 3.1% experiencing a major bleed compared to 1.9% of those receiving aspirin alone (HR=1.70; 95% CI, 1.40-2.05; $p < 0.001$). This was mainly due to an increase in bleeding leading to hospitalization, with most bleeding occurring in the gastrointestinal (GI) tract. Importantly, there was no significant difference in fatal bleeds, intracranial bleeds, symptomatic bleeding into a critical organ or bleeding into the surgical site requiring reoperation between the two groups, though the study was underpowered to detect these differences and the hazard ratios were higher compared to aspirin alone.
- The effects of the XARELTO®/aspirin regimen compared to aspirin alone on the primary outcome and on major bleeding were consistent among subgroups that were defined according to age, sex, geographic region, race or ethnic group, body weight, renal function, and history of cardiovascular risk factors.

[Click to Tweet: Robust stroke and CV death reduction in pts with stable #CAD #PAD observed in COMPASS @ #ESCCongress](#)

"COMPASS is the only clinical study to investigate the use of a Factor Xa inhibitor in people with stable CAD and PAD. The study embodies everything the EXPLORER program represents, which is to alleviate the burden felt by millions at high risk of having a major CV event," said James F. List, MD, PhD, Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen. "The combination regimen of the XARELTO® 2.5 mg vascular dose and aspirin holds much promise for these patients, and we look forward to discussing these meaningful and significant data with the U.S. Food & Drug Administration."

Researchers also presented results from the XARELTO® 5 mg twice daily group. Of patients taking XARELTO® 5 mg twice daily, 4.9% experienced a major CV event compared to 5.4% of those receiving

aspirin alone (HR=0.90; 95% CI, 0.79-1.03; p=0.12). These results were not statistically significant. Major bleeding was increased in the XARELTO® 5 mg twice daily group compared to aspirin alone (2.8% vs. 1.9%; HR=1.51; 95% CI, 1.25-1.84; p<0.001).

PAD Subgroup Analysis

Presented during the same Hot Line session at the ESC Congress 2017, a separate subgroup analysis examined patients with PAD, comprising 27.3% of the total enrollment in COMPASS. In patients with PAD in COMPASS, the combination regimen of the XARELTO® 2.5 mg twice-daily vascular dose and aspirin 100 mg once daily significantly reduced the combined risk of CV death, heart attack and stroke by 28% compared to aspirin alone (5.1% vs. 6.9%; HR=0.72; 95% CI, 0.57-0.90; p=0.005). Most notably, patients with PAD taking the XARELTO®/aspirin regimen had significantly fewer major adverse limb events by 46% (1.2% vs. 2.2%; HR=0.54; 95% CI, 0.35-0.84; p=0.005), acute limb ischemia by 44% (0.8% vs. 1.4%; HR=0.56; 95% CI, 0.32-0.99; p=0.04) and major amputations by 70% (0.2% vs 0.7%; HR=0.30; 95% CI, 0.11-0.80; p=0.01) compared to those taking aspirin alone.

"People with PAD are generally at higher risk of CV events, including death, and have fewer medical options available than patients with CAD alone, making these results exceptionally meaningful," added Dr. Eikelboom.

[Click to Tweet: Fewer amputations for stable #PAD pts, COMPASS researchers say @ #ESCCongress](#)

About COMPASS

Sponsored by Bayer and independently managed by the Population Health Research Institute (PHRI), COMPASS was conducted at 602 centers in 33 countries. Lipid-lowering agents were used by 89.8% and ACE inhibitors or angiotensin-receptor blockers were used by 71.2% of patients in the study. Mean age of study participants was 68.2 years; 22% were female. Of those enrolled, 90.6% had a history of CAD while 27.3% had a history of PAD. Patients who underwent coronary artery bypass grafting (CABG) surgery were randomized between days four and 14 after surgery. All participants were seen at one and six months after randomization, and every six months thereafter. Mean duration of patient follow-up was 23 months.

The primary efficacy endpoint was the composite of major CV events, including heart attack, stroke or CV death. The primary safety endpoint was a modification of the ISTH (International Society on Thrombosis and Haemostasis) criteria for major bleeding, and included a composite of fatal bleeding, symptomatic

bleeding into a critical organ or bleeding into the surgical site requiring reoperation, or bleeding leading to hospitalization (including presentation at an acute care facility without an overnight stay).

Secondary efficacy endpoints included the composite of coronary heart disease death, heart attack, stroke or acute limb ischemia (ALI); composite of cardiovascular death, stroke, heart attack or ALI; and all-cause mortality. Net clinical benefit also was assessed examining the composite of CV death, stroke, heart attack, fatal bleeding or symptomatic bleeding in a critical organ.

With upper GI bleeding being the most common complication in people taking antithrombotic therapy like XARELTO®, COMPASS also examined the safety and efficacy of pantoprazole, a proton pump inhibitor (PPI), compared to placebo in preventing upper GI complications in patients taking XARELTO®. This part of the study is still ongoing. Of the 27,395 patients enrolled in COMPASS, 17,597 were not receiving a PPI at the time of enrollment and were therefore enrolled into the pantoprazole arms of the study.

About EXPLORER

The EXPLORER program is unmatched by any oral anticoagulant in the Factor Xa inhibitor class in its size, scope and ambition. A collaborative effort between Janssen and Bayer, EXPLORER seeks to generate important clinical evidence on the safety and efficacy of XARELTO® and its potential role in addressing critical unmet medical needs. A number of the studies, including COMPASS, are designed to seek additional indications or expand the label for XARELTO® to benefit more patients in need of additional therapies for their cardiovascular disease. By the time of its completion, more than 275,000 patients will have participated in the EXPLORER clinical development program, other completed and ongoing clinical trials, investigative registries and non-interventional studies.

More on CAD and PAD

CAD and PAD are common circulatory conditions. One-third to one-half of all middle-aged men and women in high-income countries are at risk of developing CAD during their lifetime.^{iv} And, globally, screening studies suggest that approximately 20% of adults older than 55 years have evidence of PAD.^v

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.

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®, 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:

- **Atrial Fibrillation:** 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® once or twice a day as prescribed by your doctor.
 - Take XARELTO® with food at the same time each day.
 - If you miss a dose of XARELTO®:
 - **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.

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. 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 development of 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 January 1, 2017, including under "Item 1A. Risk Factors," its most recently filed Quarterly Report on Form 10-Q, including under the caption "Cautionary Note Regarding Forward-Looking Statements," 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 or Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

ⁱ *Circulation*. 2017; CIR.0000000000000485;ii *AHA Statistical Update*, Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association, Originally published January 25, 2017, page 360, downloaded from <http://circ.ahajournals.org/content/early/2017/01/25/CIR.0000000000000485>

ⁱⁱ *Circulation*. 2017; CIR.0000000000000485;ii *AHA Statistical Update*, Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association, Originally published January 25, 2017, page 408, downloaded from <http://circ.ahajournals.org/content/early/2017/01/25/CIR.0000000000000485>

ⁱⁱⁱ Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010;304:1350-7.

^{iv} Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet* 1999;353:89-92.

^v Hankey GJ, Norman PE, Eikelboom JW. Medical Treatment of Peripheral Arterial Disease. *JAMA* 2006;295(5):547-553.