New Data From Two Large Studies Reinforce Effectiveness of Dual Pathway Inhibition (DPI) with XARELTO® (rivaroxaban) Plus Aspirin in Patients with Coronary Artery Disease (CAD) and/or Peripheral Artery Disease (PAD)

COMPASS open label extension study results support the long-term use of XARELTO® plus aspirin for vascular protection in patients with chronic CAD and/or PAD

XATOA registry provides further evidence of the benefit of DPI for CAD and/or PAD patients at high risk of cardiovascular (CV) events

RARITAN, N.J., May 23, 2022 – Findings from the XARELTO® (rivaroxaban) Phase 3 COMPASS Long-Term Open Label Extension (LTOLE) study and the XARELTO® in Combination with Acetylsalicylic Acid (XATOA) registry were published in the European Society of Cardiology’s (ESC) European Heart Journal, Cardiovascular Pharmacotherapy. Additionally, the XATOA registry was presented at the American Congress of Cardiology’s 71st Annual Scientific Session (ACC.22). These studies provide further evidence supporting the role of dual pathway inhibition (DPI) with the XARELTO® vascular dose (2.5 mg twice daily plus aspirin 100 mg once daily) in patients with CAD and/or PAD.

The COMPASS LTOLE study found that continued treatment with XARELTO® 2.5 mg twice daily plus aspirin 75 to 100 mg once daily for up to three years was associated
with similar or lower incidence rates for major cardiovascular events (MACE) - cardiovascular (CV) death, stroke, or myocardial infarction (MI) - and for bleeding than those seen during the randomized treatment phase. Separately, the XATOA registry provides real-world evidence of the benefit of DPI with the XARELTO® vascular dose in patients with CAD and/or PAD.

Patients with CAD and/or PAD are at risk of secondary thrombotic events associated with CV disease including stroke, MI, ischemic limb events, and CV-related death.¹ Antiplatelet therapies, such as aspirin, are used to help prevent thrombosis by inhibiting platelet aggregation.¹ Antithrombotic therapy is often recommended in addition to an antiplatelet therapy (commonly aspirin) – known as DPI – to further reduce residual risk of CV events in certain patients with CAD and/or PAD.² The XARELTO® vascular dose (2.5 mg twice daily plus aspirin 100 mg once daily) is the first and only approved treatment for CAD and PAD using a DPI approach to target both clotting mechanisms – thrombin generation and platelet activation.

“What we saw initially in COMPASS, and now again with its long-term open label continuation study, is that dual-pathway inhibition with XARELTO® plus aspirin can significantly reduce the underlying thrombotic risk of cardiovascular events in patients with CAD and/or PAD,” said James F. List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular, Metabolism, and Retina, Janssen Research & Development, LLC. “Additionally, through the real-world XATOA registry, we’ve now uncovered, for the first-time, which types of patients are most often selected for and may benefit from dual pathway inhibition. These data provide practical, clinical insights to those who treat these difficult conditions.”

**COMPASS LTOLE results support long-term use of XARELTO® plus aspirin**

COMPASS, the largest clinical trial of XARELTO® to date with 27,395 patients, showed that the XARELTO® vascular dose reduced the risk of major CV events by 24 percent in patients with chronic CAD and/or PAD. Of the patients originally randomized in COMPASS, 12,964 were subsequently enrolled in the LTOLE study to investigate the long-term use of XARELTO® plus aspirin for up to three years.
The findings showed that XARELTO® 2.5 mg twice daily plus aspirin 75 mg to 100 mg once daily was associated with a primary outcome event rate (CV death, stroke or MI) of 2.35 (95% CI 2.11-2.61 per 100 patient years; n=353), which was similar to the rate observed during the randomized treatment phase (2.18 [95% CI 1.97-2.41] per 100 patient years; n=379). Major bleeding rates during LTOLE had an incidence rate of 1.01 [95% CI 0.86-1.19], whereas the randomized phase showed major bleeding of 1.67 [95% CI 1.48-1.87] per 100 patient years. The COMPASS randomized clinical trial results were previously published in the *New England Journal of Medicine* in 2017, which confirmed the safety profile of XARELTO® plus aspirin.

“When first presented, the COMPASS results represented a real breakthrough in CAD and PAD, as they confirmed the XARELTO® vascular dose is effective in helping to prevent the detrimental cardiovascular events that often occur in these patients,” said Professor John Eikelboom*, McMaster University in Hamilton, Canada, and lead author of the COMPASS and LTOLE studies. “It’s extremely reassuring to see that these benefits continue long-term, as observed in our open label extension study.”

The COMPASS LTOLE study was not randomized and did not include a control group. Only 47 percent of the original COMPASS cohort entered LTOLE, thereby introducing potential selection and survival biases. Patients who were entered into LTOLE are not directly comparable to those who were originally randomized in the COMPASS trial as the two cohorts are overlapping and patients enrolled in LTOLE are several years older.

**Real-world XATOA registry reconfirms findings from COMPASS**

The XATOA registry investigated the clinical characteristics in CAD and/or PAD patients prescribed DPI using XARELTO® 2.5 mg plus aspirin and reported the clinical outcomes and bleeding rates in clinical practice compared to the COMPASS randomized trial. The XATOA registry helps provide clinicians additional information on which types of patients may benefit from DPI therapy in clinical practice.

The full analysis set consisted of 5,532 patients with CAD and/or PAD who received at least one dose of DPI with XARELTO® 2.5 mg and aspirin. Of the patients in the full analysis set, 4,022 (72.7%) had CAD, 3,258 (58.9%) had PAD, and 1,748 (31.6%)
had both CAD and PAD. The average observation period in the full analysis set was 15±6 months and 79.1% (n = 4,374) were followed up for more than 12 months.

The results found the most frequently reported reason for initiating DPI was the presence of existing, worsening or newly diagnosed risk characteristics (n = 4753, 85.9%). The rates of MACE were similar to those in the COMPASS trial (2.26 vs 2.18 per 100 patient years) and rates of major adverse limb events (MALE) were higher (3.57 vs 0.19), consistent with the greater proportion of patients with PAD in the study. The study also showed that major bleeding occurred at a rate of 0.95 (per 100 patient years) compared to 1.7 (per 100 patient years) in the COMPASS trial.

“For the first time, we’ve uncovered which patient characteristics go into a physician’s decision making for prescribing dual-pathway treatment to help reduce the risk of major cardiovascular events,” said Professor Keith Fox**, University of Edinburgh, and lead author of the XATOA registry. “In the XATOA registry, patients who received treatment with XARELTO® plus aspirin had outcomes consistent with the COMPASS study. These real-world findings help support the use of DPI in patients at increased risk of vascular events.”

Patients enrolled in the XATOA registry were screened consecutively to reduce selection bias and measures were taken to ensure that the enrolled patients were representative of the population of each study site. As outcomes were collected in different ways in XATOA and COMPASS, differences between outcomes in the studies are inherent.

About CAD and PAD
Cardiovascular diseases (CVD), including coronary artery disease (CAD) and peripheral artery disease (PAD), account for around 1 in every 3 deaths worldwide.3 Despite advances in management, CVDs continue to place a significant burden on healthcare, social care, and financial systems.4 CAD, or ischemic heart disease, is the most common type of heart disease, affecting approximately 18.2 million adults in the U.S.5 PAD is a common chronic circulatory condition that causes blood vessels to narrow, thereby reducing blood flow to the limbs, and most often the legs.6 It is a disease which often goes undiagnosed and undertreated.7 In the U.S., PAD affects an estimated 20 million adults, yet only approximately 8.5 million are diagnosed.8,9
About the XATOA Study
XATOA was an international, multi-center, prospective, single-arm study designed to provide insights into the clinical characteristics of patients selected for DPI with CAD, PAD or both and their clinical outcomes and bleeding rates in clinical practice. 5,532 patients were included, and most were treated only with aspirin prior to enrollment.

Clinical outcomes of interest included major adverse cardiovascular events (MACE), and major adverse limb events (MALE). The safety outcome was the International Society on Thrombosis and Haemostasis (ISTH) major bleeding. Outcome definitions were harmonized with those of the COMPASS study to allow comparisons of the data.

About the COMPASS and COMPASS LTOLE Studies
In the double-blind part of the Phase III COMPASS study the vascular dose of XARELTO® (2.5 mg twice daily plus aspirin 100 mg once daily) reduced the risk of stroke, myocardial infarction, or cardiovascular death and all-cause mortality in patients receiving a high standard of risk factor management for CAD and/or PAD. The treatment resulted in a relative risk reduction of 42 percent in stroke and 22 percent in cardiovascular death compared with aspirin 100 mg once daily alone. Bleeding rates were low, and while major bleeding increased, notably there was no significant increase in intracranial or fatal bleeding.

Of the patients originally randomized in COMPASS, 12,964 were subsequently enrolled in the open-label extension part, from 455 sites in 32 countries. All patients received XARELTO® 2.5 mg twice daily plus aspirin 75 to 100 mg once daily for a median of 374 days. They were followed every 6 months to evaluate adherence and safety, and to collect clinical outcomes, including stroke, MI, and mortality.

The COMPASS study was a collaboration between Bayer, Janssen Research & Development, LLC and the Population Health Research Institute (PHRI), a joint institute of McMaster University and Hamilton Health Sciences.

WHAT IS XARELTO® (rivaroxaban)?
XARELTO® is a prescription medicine used to:

- reduce the risk of stroke and blood clots in adults 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 adults 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 adults who have just had hip or knee replacement surgery
- help prevent blood clots in certain adults hospitalized for an acute illness and after discharge, who are at risk of getting blood clots because of the loss of or decreased ability to move around (mobility) and other risks for getting blood clots, and who do not have a high risk of bleeding

XARELTO® is used with low dose aspirin to:

- reduce the risk of serious heart problems, heart attack and stroke in adults with coronary artery disease (a condition where the blood supply to the heart is reduced or blocked)
- reduce the risk of a sudden decrease in blood flow to the legs, major amputation, serious heart problems or stroke in adults with peripheral artery disease (a condition where the blood flow to the legs is reduced) and includes adults who have recently had a procedure to improve blood flow to the legs

XARELTO® is used in children to:

- treat blood clots or reduce the risk of blood clots from happening again in children from birth to less than 18 years, after receiving at least 5 days of initial treatment with injectable or intravenous medicines used to treat blood clots.
- help prevent blood clots in children 2 years and older with congenital heart disease after the Fontan procedure.

XARELTO® was not studied and is not recommended in children less than 6 months of age who:

- were less than 37 weeks of growth (gestation) at birth
- had less than 10 days of oral feeding, or
- had a body weight of less than 5.7 pounds (2.6 kg)

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 heartbeat) 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 be at higher risk of bleeding if you take XARELTO® and have certain other medical problems.

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 or your child 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
  o Bleeding that is severe or you cannot control
  o Red, pink, or brown urine
  o Bright red or black stools (looks like tar)
  o Cough up blood or blood clots
  o Vomit blood or your vomit looks like "coffee grounds"
  o Headaches, feeling dizzy or weak
  o 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:
  o A thin tube called an epidural catheter is placed in your back to give you certain medicine
  o You take NSAIDs or a medicine to prevent blood from clotting
  o You have a history of difficult or repeated epidural or spinal punctures
  o 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 use in people with artificial heart valves.

XARELTO® is not for use in people with antiphospholipid syndrome (APS), especially with positive triple antibody testing.

**Do not take XARELTO® if you or your child:**

• 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 or your child:**

• Have ever had bleeding problems
• Have liver or kidney problems
• Have antiphospholipid syndrome (APS)
• Are pregnant or plan to become pregnant. It is not known if XARELTO® will harm your unborn baby.
  o **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.
  o Females who are able to become pregnant: Talk with your doctor about pregnancy planning during treatment with XARELTO®. Talk with your doctor about your risk for severe uterine bleeding if you are treated with blood thinner medicines, including XARELTO®.
  o 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. Talk to your doctor about the best way to feed your baby during treatment with XARELTO®.

Tell all of your doctors and dentists that you or your child 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 or your child 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.
• Your doctor will decide how long you should take XARELTO®.
• XARELTO® may need to be stopped for one or more days before any surgery or medical or dental procedure. Your doctor will tell you when to stop taking XARELTO® and when to start taking XARELTO® again after your surgery or procedure.
• If you need to stop taking XARELTO® for any reason, talk to the doctor who prescribed XARELTO® to you to find out when you should stop taking it. Do not stop taking XARELTO® without first talking to the doctor who prescribes it to you.
• If you have difficulty swallowing XARELTO® tablets whole, talk to your doctor about other ways to take XARELTO®.
• Do not run out of XARELTO®. Refill your prescription of XARELTO® before you run out. When leaving the hospital following a hip or knee replacement, be sure that you will 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.

If you take XARELTO® for:
  o 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.
  o 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 10-mg dose, XARELTO® may be taken with or without food.
    ▪ For the 15-mg and 20-mg doses, take XARELTO® with food 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.
  o 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.
  o Blood clots in people hospitalized for an acute illness:
    ▪ Take XARELTO® 1 time a day, with or without food, while you are in the hospital and after you are discharged as prescribed by your doctor.
    ▪ 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.
  o Reducing the risk of serious heart problems, heart attack and stroke in coronary artery disease:
    ▪ Take XARELTO® 2.5 mg 2 times a day with or without food.
    ▪ If you miss a dose of XARELTO®, take your next dose at your regularly scheduled time.
    ▪ Take aspirin 75 to 100 mg once daily as instructed by your doctor.
  o Reducing the risk of a sudden decrease in blood flow to the legs, major amputation, serious heart problems or stroke in people with peripheral artery disease, including those who have recently had a procedure to improve blood flow to the legs:
▪ Take XARELTO® 2.5 mg 2 times a day with or without food.
▪ If you miss a dose of XARELTO®, take your next dose at your regularly scheduled time.
▪ Take aspirin 75 to 100 mg once daily as instructed by your doctor.

For children who take XARELTO®:
  o The dose of XARELTO® depends on your child’s body weight and will be calculated by your child’s doctor. Your child’s doctor will tell you if XARELTO® can be given to your child with or without food.
  o The adult caregiver should give the dose.
  o If your child is taking the tablet, the tablet should be taken whole and should not be split in an attempt to provide a lower dose of XARELTO®.
  o If your child is taking the oral suspension, use the syringes provided in the original carton. The suspension will be prepared by the pharmacy. See the Instructions for Use included in the carton on how to properly give a dose of XARELTO® oral suspension to your child.
  o Do not switch between the XARELTO® oral suspension or tablet without first talking to your doctor.
  o If your child vomits or spits up:
    ▪ right after or within 30 minutes of taking the oral suspension, give a new full dose.
    ▪ more than 30 minutes after taking the oral suspension, do not give the dose again. Give the next dose at the regularly scheduled time.
    ▪ if vomiting or spitting up persists, contact your child’s doctor right away.
  o If your child misses a dose:
    ▪ If your child is taking XARELTO® 1 time a day, give the dose as soon as you remember on the same day. If this is not possible, skip this dose and give the next dose at the regularly scheduled time.
    ▪ If your child is taking XARELTO® 2 times a day, give the missed morning dose as soon as you remember. You may give the missed morning dose together with the evening dose. However, a missed evening dose can only be taken in the same evening.
    ▪ If your child is taking XARELTO® 3 times a day, skip the missed dose and give the next dose at the regularly scheduled time.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF XARELTO®?

XARELTO® may cause serious side effects:
  • See “What is the most important information I should know about XARELTO®?”

The most common side effect of XARELTO® in adults was bleeding.

The most common side effects of XARELTO® in children include:
  • bleeding
  • vomiting
  • cough
- inflamed stomach and gut

Call your doctor for medical advice about side effects. You may report side effects to the 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 read full Prescribing Information, including Boxed Warnings, and Medication Guide for XARELTO®.

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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.


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 and the potential benefits and treatment impact of 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 Research & Development, LLC, 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 2, 2022, including in the sections captioned “Cautionary Note Regarding Forward-Looking Statements” and “Item 1A. Risk Factors,” and in Johnson & Johnson’s subsequent Quarterly Reports on Form 10-Q and other 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.

2 Fox, K, Aboyans, V, Debus, ES, et al. Patients selected for dual pathway inhibition in clinical practice have similar characteristics and outcomes to those included in the COMPASS randomized trial: The XATOA Registry. European Heart Journal - Cardiovascular Pharmacotherapy. 2022 [Insert doi once live]
* John Eikelboom is the lead author of the COMPASS trial and LTOLE study. He is affiliated with the Population Health Research Institute, Hamilton Health Sciences and McMaster University. The Population Health Research Institute was provided a grant for their participation in both studies.
** Keith Fox is the lead author of the XATOA registry and has received compensation.