Media contacts:
Joy-Lee Pasqualoni
Mobile: (917) 547-8078
LPasqua7@its.jnj.com

Jennifer Silvent
Mobile: (973) 479-9845
JSilvent@its.jnj.com

Investor contacts:
Johnson & Johnson
Christopher DelOrefice
Office: (732) 524-2955

Jennifer McIntyre
Office: (732) 524-3922

Janssen Submits Application to U.S. FDA for New Indication to Expand Use of XARELTO® (rivaroxaban) in Patients with Peripheral Artery Disease

Application seeks approval of XARELTO® plus aspirin to reduce the risk of major thrombotic vascular events in patients after lower-extremity revascularization due to symptomatic peripheral artery disease (PAD)

XARELTO® is currently approved to reduce the risk of major cardiovascular events, like heart attack and stroke, in people with chronic PAD

An estimated 20 million Americans are living with PAD, a disease often underdiagnosed and undertreated

RARITAN, NJ, October 26, 2020 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today it has submitted a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) for a new indication to expand the use of XARELTO® (rivaroxaban) in patients with peripheral artery disease (PAD). If approved, this new indication for the XARELTO® vascular dose (2.5 mg twice daily plus aspirin 75-100 mg once daily) would include reducing the risk of major thrombotic vascular events such as heart attack, stroke and amputation in patients after recent lower-extremity revascularization, a common

procedure in which blood flow is restored to the legs and feet due to symptomatic PAD. The application is based on data from the VOYAGER PAD study, which showed XARELTO® (2.5 mg twice daily) plus aspirin (100 mg once daily) was superior to aspirin alone in reducing the risk of major cardiovascular (CV) and limb events, with similar rates of Thrombolysis In Myocardial Infarction (TIMI) major bleeding.

CLICK TO TWEET: @JanssenUS announces sNDA submission to @US_FDA in #peripheralarterydisease #PAD. Learn more: http://bit.ly/XXXXXXX.

"Various antithrombotic regimens have been evaluated for short- and long-term prevention of major vascular events in patients with PAD, but only rivaroxaban in combination with aspirin has demonstrated a significant benefit over aspirin alone," said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen Research & Development, LLC. "Data from the VOYAGER PAD trial were the first in 20 years to show clinical benefit with an antithrombotic therapy in the symptomatic PAD population after lower-extremity revascularization, which speaks to the need for a new treatment in this space. We look forward to discussing these data with the FDA."

Janssen and its development partner Bayer have conducted two major Phase 3 trials, VOYAGER PAD and COMPASS, that evaluated the use of dual antithrombotic pathway inhibition with XARELTO® plus aspirin in patients with PAD. XARELTO®, in combination with aspirin, was approved by the FDA in 2018 to reduce the risk of major CV events in patients with chronic PAD and coronary artery disease (CAD) – the only direct oral anticoagulant (DOAC) approved for use in these populations.

PAD is a serious underlying health crisis that impacts an estimated 20 million Americans, with only 8.5 million diagnosed.[i,ii] PAD also increases the risk for major CV events and is the leading cause of amputation,[iii] which can double a patient's risk of death.[iv]

About VOYAGER PAD

The Phase 3 VOYAGER PAD study included 6,564 patients from 542 sites across 34 countries worldwide. Patients were randomized in a 1:1 ratio and received either XARELTO® (2.5 mg twice daily) plus aspirin (100 mg once daily) (n=3,286) or aspirin alone (100 mg once daily) (n=3,278). Patients were stratified by revascularization procedure type (endovascular vs. surgical) and use of clopidogrel, which was limited and administered based on the treating physician's discretion. Patients were followed for a median duration of 28 months.

The primary efficacy endpoint was a composite of major adverse limb and CV events, including acute limb ischemia, major amputation for vascular causes, heart attack (myocardial infarction), ischemic stroke, or death from CV causes. The principal safety endpoint was major bleeding according to the TIMI classification.

Eligible patients were at least 50 years old and had documented symptomatic lower-extremity PAD. Patients were eligible after a successful revascularization for symptomatic PAD within the last 10 days. Approximately two-thirds were treated with an endovascular procedure (65%) and one-third treated surgically (35%). Patients were excluded if they were clinically unstable, at heightened bleeding risk, or needed prohibited concomitant medications, including long-term clopidogrel. The median age was 67 years and 26% were women. Common risk factors for PAD included diabetes, an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 (indicating mild-to-moderate kidney disease) and current smokers.

WHAT IS XARELTO® (rivaroxaban)?

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
- help prevent blood clots in certain people 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 people with coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) or peripheral artery 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 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 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 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:

- 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
- Have antiphospholipid syndrome (APS)
- 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. 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 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.
- 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:

- **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 **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.
- **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.
  - **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.
  - **Reducing the risk of serious heart problems, heart attack and stroke in coronary artery disease or peripheral 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.

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® was bleeding.

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®.

About Janssen Cardiovascular & Metabolism

In Cardiovascular & Metabolism (CVM), we take on the most pervasive diseases that burden hundreds of millions of people and healthcare systems around the world. As part of this long-standing commitment and propelled by our successes in treating type 2 diabetes and thrombosis, we advance highly differentiated therapies that prevent and treat life-threatening cardiovascular, metabolic and retinal diseases. Uncovering new therapies that can improve the quality of life for this large segment of the population is an important endeavor – one which Janssen CVM will continue to lead in the years to come. Our mission is global, local and personal.

Together, we can reshape the future of cardiovascular, metabolic and retinal disease prevention and treatment. Please visit www.janssen.com/cardiovascular-and-metabolism.

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/JanssenUS and https://twitter.com/JanssenGlobal. Janssen Research & Development, LLC, is one 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 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 December 29, 2019, 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] Racial Disparities in Vascular Care. (n.d.). Retrieved October 2, 2020, from https://cardiovascularcoalition.com/our-patients/racial-disparities-in-vascular-care/

[ii] Centers for Disease Control and Prevention. Peripheral Arterial Disease Fact Sheet/Data & Statistics. Retrieved March 20, 2020 from: https://www.cdc.gov/heartdisease/pad.htm.

[iii] Norgren L, Hiatt WR, Dormandy JA, Hirsch AT, et al. The next 10 years in the management of peripheral artery disease: perspectives from the 'PAD 2009' Conference. *Eur Vasc Endovasc Surg.* 2010;40(3):375-380.

[iv] Jones WS, Patel MR, Dai D, et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J.* 2013;165(5):809-815.