XARELTO® (rivaroxaban) Reduces Recurrent Blood Clots and Total Medical Costs in Morbidly Obese Patients

New real-world study of patients with venous thromboembolism (VTE) and morbid obesity shows safety and effectiveness of XARELTO® were similar to warfarin, with significantly less healthcare resource utilization (HRU) and total medical costs.

TITUSVILLE, N.J., September 20, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today important new real-world evidence confirming XARELTO® (rivaroxaban) reduced the risk of recurrent venous thromboembolism (VTE) – or blood clots – in patients who are morbidly obese, with effectiveness and safety similar to warfarin. Notably, patients taking XARELTO® had significantly reduced healthcare resource utilization (HRU) and total medical costs compared to those taking warfarin. Results of this study were recently published in Thrombosis Research.

Click to Tweet: New real-world study of patients with #bloodclots and morbid #obesity shows #DOAC had similar safety and effectiveness, and less costs than warfarin http://po.st/OwDWlM
Approximately 40 percent of the U.S. population have obesity and about 8 percent have morbid obesity. Obesity increases the risk of VTE by two- to six-fold compared with non-obese patients. Typically, morbidly obese patients are treated with older anticoagulants, such as warfarin, and require more laboratory monitoring than patients of normal weight. In addition, morbidly obese patients are often underrepresented in Phase 3 studies.

“This is the first large-scale, real-world study to evaluate a direct oral anticoagulant (DOAC) in morbidly obese patients with VTE, and the first to identify healthcare resource utilization and medical costs in this population,” said Alex C. Spyropoulos, M.D., Professor of Medicine, The Donald and Barbara Zucker School of Medicine, Hofstra University, Northwell Health at Lenox Hill Hospital, New York, N.Y. “We now know from this research that rivaroxaban is as effective and safe as dose-adjusted warfarin when treating morbidly obese patients, without the need for routine anti-Xa measurements, and with significantly lower healthcare resource utilization. Physicians should feel confident in prescribing rivaroxaban for managing VTE in this population.”

In 2016, the International Society on Thrombosis and Haemostasis (ISTH) published a guidance statement recommending against DOAC use in morbidly obese patients. This recommendation was based on limited clinical data and concerns about available pharmacokinetic/pharmacodynamic (PK/PD) evidence from another DOAC that suggested a decrease in drug levels with increased body weight. Published data for XARELTO®, however, found that the medicine’s PK/PD were not meaningfully influenced by body weight, and this research is reflected in the XARELTO® prescribing information.

“Obesity affects millions of Americans and is a significant risk factor for VTE and NVAF,” said Paul Burton, M.D., Ph.D., FACC, Vice President, Medical Affairs, Internal Medicine, Janssen Scientific Affairs, LLC. “These real-world studies, coupled with the

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1 Dr. Alex Spyropoulos worked directly with Janssen Scientific Affairs, LLC and was compensated for his work on this study.
consistent PK/PD and clinical data for XARELTO® in obese patients with VTE or NVAF, underpin the broad clinical utility of XARELTO® and provide clinicians with the evidence to consider an alternative option to warfarin.”

Study Results
More than 5,000 morbidly obese patients (those who had a body mass index [BMI] of ≥40) were included in the study, with half receiving XARELTO® and half receiving warfarin. There were 2,890 matched pairs in the intent-to-treat (ITT) analysis and 2,832 pairs in the on-treatment analysis. The following observations for the ITT analysis were made:

- **Recurrent VTE**: The risk of recurrent VTE was not significantly different between XARELTO® and warfarin (16.8 percent vs. 15.9 percent; Odds Ratio [OR]: 0.99; 95 percent confidence interval [CI]: 0.85 to 1.14; p=0.8443).
- **Major Bleeding**: The study found significantly fewer major bleeding events for those taking XARELTO® compared to those taking warfarin (1.8 percent vs. 2.5 percent; OR: 0.66; 95 percent CI: 0.45 to 0.98; p=0.0388).
- **HRU**: XARELTO® was associated with significantly lower HRU compared to treatment with warfarin. Specifically, hospitalizations occurred in 35.1 percent and 38.6 percent, respectively (OR: 0.86; 95 percent CI: 0.77 to 0.96; p=0.0057). XARELTO® patients, on average, had 19 fewer per patient per year (PPPY) outpatient visits, including laboratory encounters, compared to warfarin-treated patients (93 vs. 112 encounters; p<0.0001).
- **Medical Costs**: XARELTO® treatment yielded significantly less HRU and total medical costs (hospitalizations, emergency room, outpatient and office visits, skilled nursing facility/long-term care), with similar total healthcare costs (including total medical costs and pharmacy costs) between groups. Average total medical costs PPPY were $2,829 lower with XARELTO® compared to

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2 For the ITT analysis, patients were followed until the first event of interest or until the end of the 12-month observation period.
3 For the on-treatment analysis, patients were followed from treatment initiation to discontinuation.
warfarin ($34,824 vs. $37,653; p=0.0201), which were mainly driven by hospitalization costs.

The on-treatment analysis found no significant differences for recurrent VTE and major bleeding between XARELTO® and warfarin, with significantly lower HRU and total medical costs associated with XARELTO®.

The results of this VTE study are consistent with data across body weightsiii from the EINSTEIN DVT and EINSTEIN PE randomized clinical trials, which were the Phase 3 registration trials for XARELTO® in VTE (deep vein thrombosis or DVT, and pulmonary embolism or PE). Additionally, this real-world VTE study complements the only other large-scale, real-world studyiv of over 7,000 patients with NVAF and morbid obesity where consistent effectiveness, safety and reduction in healthcare and total medical costs with XARELTO® were shown. The safety and effectiveness align with what was observed in ROCKET AF, the Phase 3 registration trial for XARELTO® in NVAF.

**Study Background**

This retrospective study analyzed data from two U.S. claims databases (Truven MarketScan Commercial Claims and Encounters database and MarketScan Medicare Supplemental database). Adult patients who had one or more medical claims with a VTE diagnosis between December 1, 2012 and September 30, 2016 were eligible for the study. Of these patients, those who initiated treatment with XARELTO® or warfarin within 28 days of VTE diagnosis and had at least one diagnosis of morbid obesity were included. Researchers utilized propensity score matching to create 2,890 matched pairs of patients who initiated treatment with either XARELTO® or warfarin. Most patients in the XARELTO® cohort initiated treatment with the 15 mg twice-daily dose.

The study included two analyses: ITT and on-treatment. The primary outcome was the risk of recurrent VTE, defined as a hospitalization or ER visit with a primary
diagnosis of VTE during the follow-up period. Secondary outcomes included major bleeding risk, HRU and costs.

Participants were ineligible if they had a diagnosis of VTE or atrial fibrillation at any time prior to the treatment initiation, or if they had an oral anticoagulant prescription prior to treatment initiation.

All real-world studies have limitations. This study was a retrospective claims analysis with inherent limitations. In this study, the use of administrative claims data may have been coded incorrectly or inconsistently. Residual confounding due to unmeasured confounders not included in the propensity match could not be fully excluded. A claim for a prescription does not necessarily indicate that the medication was taken. The use of diagnosis codes to identify patients who have morbid obesity may have been underestimated as height and weight were not available to confirm body mass index status.

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 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 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, who have a history of blood clots.

**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.

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

**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 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.

Trademarks are those of their respective owners. Janssen and Bayer together are developing rivaroxaban. For more information about XARELTO®, visit [www.xarelto.com](http://www.xarelto.com).

**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 (T2D) 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, and 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](http://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.


**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 Scientific Affairs, 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 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. Neither 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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