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Janssen Submits Supplemental New Drug Application (sNDA) to FDA for XARELTO® (rivaroxaban) to Prevent Venous Thromboembolism (VTE) in Acute Medically Ill Patients

If approved, this will add to the five existing VTE indications for XARELTO® – the most studied anticoagulant available to the most groups of patients

Despite being largely preventable, VTE remains a significant risk for the eight million Americans with acute medical illnesses

TITUSVILLE, NJ (December 14, 2018) – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today the submission of a supplemental New Drug Application (sNDA) for XARELTO® (rivaroxaban) to the U.S. Food and Drug Administration (FDA) for the prevention of venous thromboembolism (VTE), or blood clots, in medically ill patients. This application is based on combined data from the Phase 3 MAGELLAN and MARINER trials, which evaluated XARELTO® for the prevention of VTE in these patients during their hospital stay and immediately following discharge.

Click-to-Tweet: ***Janssen submits application to FDA to expand the use of its #bloodthinner for #VTE #bloodclot prevention in acute medically ill patients https://ctt.ec/G6de0+***

Approximately eight million Americans are hospitalized each year for acute medical illnesses, which include serious yet common conditions like heart failure, stroke, respiratory insufficiency, infectious diseases and inflammatory diseases. Hospital-associated VTE is the leading cause of premature death and disability in this population,[i] and the risk of VTE also extends to the outpatient setting. In fact, 67 percent of recently hospitalized patients who develop a VTE do so within one month of discharge.[ii] Guidelines currently recommend that people at risk of VTE receive anticoagulants in the hospital but advise against routine anticoagulant use beyond the hospital stay.

"Despite being at high risk of VTE for up to six weeks when leaving the hospital, less than four percent of patients[iii] with acute medical illnesses are prescribed anticoagulant therapy to prevent VTE after they leave the hospital," said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen Research & Development, LLC. "We hope to make XARELTO® available for these patients to prevent a VTE for the time that they remain at risk, beginning with hospitalization through at-home recovery."

XARELTO® already has five approved VTE indications, including the treatment of deep vein thrombosis (DVT), treatment of pulmonary embolism (PE), reduction of the risk of recurrent DVT and PE, and primary prevention of DVT, which may lead to PE, in people who have just had hip or knee replacement surgery. In October 2017, the FDA approved a new dose regimen of 10 mg XARELTO® once-daily for reducing the continued risk for recurrent VTE after completion of at least six months of initial therapy.

About MAGELLAN and MARINER

Published in 2013, the Phase 3 MAGELLAN study evaluated the use of XARELTO® 10 mg in preventing VTE in acute medically ill patients, starting with their hospital stay and continuing through post-hospital discharge. The study met its two co-primary endpoints, with XARELTO® demonstrating non-inferiority to enoxaparin in short-term use (10 ± 4 days) and superiority in long-term use (35 ± 4 days) compared to short-term use of enoxaparin followed by placebo. The combined rates of major and non-major clinically relevant bleeding were higher in those treated with XARELTO®.

Building on the foundation provided by the results from MAGELLAN, the Phase 3 MARINER trial was conducted in a similar population of medically ill patients, evaluating XARELTO® for the prevention of VTE and VTE-related death following hospital discharge. While MARINER demonstrated that XARELTO® did not reduce the composite endpoint of VTE and VTE-related death, it did significantly reduce symptomatic VTE with consistent and favorable safety, reinforcing XARELTO®'s positive benefit-risk profile.

About EXPLORER

MAGELLAN and MARINER are part of the EXPLORER clinical research program for XARELTO®. A collaborative effort between Janssen and its development partner Bayer, EXPLORER has generated important clinical evidence on the safety and efficacy of XARELTO®. Many studies in the program are designed to seek additional indications or expand the label for XARELTO® to benefit more patients in need of therapies for their cardiovascular (CV) disease. By the time of its completion, more than 275,000 patients will have participated in the EXPLORER program, other completed and ongoing clinical trials, investigative registries and non-interventional studies.

WHAT IS XARELTO®?

XARELTO® is a prescription medicine used to:

- reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation that is not caused by a heart valve problem. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to the

formation of blood clots, which can travel to the brain, causing a stroke, or to other parts of the body
- treat blood clots in the veins of your legs (deep vein thrombosis or DVT) or lungs (pulmonary embolism or PE)
- reduce the risk of blood clots happening again in people who continue to be at risk for DVT or PE after receiving treatment for blood clots for at least 6 months
- help prevent a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery

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

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

IMPORTANT SAFETY INFORMATION

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

XARELTO® may cause serious side effects, including:

- **Increased risk of blood clots if you stop taking XARELTO®**.
  People with atrial fibrillation (an irregular heart beat) that is not caused by a heart valve problem (nonvalvular) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. XARELTO® lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking XARELTO®, you may have increased risk of forming a clot in your blood.
  Do not stop taking XARELTO® without talking to the doctor who prescribes it for you. Stopping XARELTO® increases your risk of having a stroke.
  If you have to stop taking XARELTO®, your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.
- **Increased risk of bleeding.** XARELTO® can cause bleeding which can be serious, and may lead to death. This is because XARELTO® is a blood thinner medicine (anticoagulant) that lowers blood clotting. During treatment with XARELTO® you are likely to bruise more easily, and it may take longer for bleeding to stop.

  You may have a higher risk of bleeding if you take XARELTO® and take other medicines that increase your risk of bleeding, including:

  - Aspirin or aspirin-containing products
  - Long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
  - Warfarin sodium (Coumadin®, Jantoven®)
  - Any medicine that contains heparin

- Clopidogrel (Plavix®)
- Selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
- Other medicines to prevent or treat blood clots

Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

Call your doctor or get medical help right away if you develop any of these signs or symptoms of bleeding:

- Unexpected bleeding or bleeding that lasts a long time, such as:
  - Nosebleeds that happen often
  - Unusual bleeding from gums
  - Menstrual bleeding that is heavier than normal, or vaginal bleeding
- Bleeding that is severe or you cannot control
- Red, pink, or brown urine
- Bright red or black stools (looks like tar)
- Cough up blood or blood clots
- Vomit blood or your vomit looks like "coffee grounds"
- Headaches, feeling dizzy or weak
- Pain, swelling, or new drainage at wound sites
- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like XARELTO®, and have medicine injected into their spinal and epidural area, or have a spinal puncture, have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - A thin tube called an epidural catheter is placed in your back to give you certain medicine
  - You take NSAIDs or a medicine to prevent blood from clotting
  - You have a history of difficult or repeated epidural or spinal punctures
  - You have a history of problems with your spine or have had surgery on your spine

If you take XARELTO® and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots. Tell your doctor right away if you have back pain, tingling, numbness, muscle weakness (especially in your legs and feet), or loss of control of the bowels or bladder (incontinence).

- **XARELTO® is not for people with artificial heart valves.**

Do not take XARELTO® if you:

- Currently have certain types of abnormal bleeding. Talk to your doctor before taking XARELTO® if you currently have unusual bleeding.
- Are allergic to rivaroxaban or any of the ingredients of XARELTO®.

Before taking XARELTO®, tell your doctor about all your medical conditions, including if you:

- Have ever had bleeding problems
- Have liver or kidney problems

- Are pregnant or plan to become pregnant. It is not known if XARELTO® will harm your unborn baby.
  - Tell your doctor right away if you become pregnant during treatment with XARELTO®. Taking XARELTO® while you are pregnant may increase the risk of bleeding in you or in your unborn baby.
  - If you take XARELTO® during pregnancy, tell your doctor right away if you have any signs or symptoms of bleeding or blood loss. **See "What is the most important information I should know about XARELTO®?" for signs and symptoms of bleeding.**
- Are breastfeeding or plan to breastfeed. XARELTO® may pass into your breast milk. You and your doctor should decide if you will take XARELTO® or breastfeed.

Tell all of your doctors and dentists that you are taking XARELTO®. They should talk to the doctor who prescribed XARELTO® for you before you have any surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way XARELTO® works, causing side effects. Certain medicines may increase your risk of bleeding. **See "What is the most important information I should know about XARELTO®?"**

HOW SHOULD I TAKE XARELTO®?

- Take XARELTO® exactly as prescribed by your doctor.
- Do not change your dose or stop taking XARELTO® unless your doctor tells you to.
- Your doctor may change your dose if needed.
- If you take XARELTO® for:
  - **Atrial Fibrillation that is not caused by a heart valve problem:**
    - Take XARELTO® **1 time a day with your evening meal**.
    - If you miss a dose of XARELTO®, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
  - **Blood clots in the veins of your legs or lungs:**
    - Take XARELTO® **1 or 2 times a day** as prescribed by your doctor.
    - For the **15-mg and 20-mg doses,** XARELTO® **should be taken with food.**
    - For the **10-mg dose**, XARELTO® **may be taken with or without food.**
    - Take your XARELTO® doses at the same time each day.
    - If you miss a dose:
      - **If you take the 15-mg dose of XARELTO 2 times a day (a total of 30 mg of XARELTO in 1 day):** Take XARELTO® as soon as you remember on the same day. You may take 2 doses at the same time to make up for the missed dose. Take your next dose at your regularly scheduled time.

        - **If you take XARELTO® 1 time a day:** Take XARELTO® as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
    - **Hip or knee replacement surgery:**
        - Take XARELTO® 1 time a day with or without food.
        - If you miss a dose of XARELTO®, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
    - **Reducing the risk of serious heart problems, heart attack and stroke in coronary artery disease or peripheral arterial disease:**
        - Take XARELTO® 2 times a day with or without food.
        - If you miss a dose of XARELTO®, take your next dose at your regularly scheduled time.
- If you have difficulty swallowing the XARELTO® tablet whole, talk to your doctor about other ways to take XARELTO®.
- Your doctor will decide how long you should take XARELTO®.
- XARELTO® may need to be stopped, if possible for one or more days before any surgery or medical/dental procedure. If you need to stop taking XARELTO® for any reason, talk to your doctor to find out when you should stop taking it. **Do not stop taking XARELTO® without first talking to the doctor who prescribed it to you.** Your doctor will tell you when to start taking XARELTO® again after your surgery or procedure.
- Do not run out of XARELTO®. Refill your prescription for XARELTO® before you run out. When leaving the hospital following a hip or knee replacement, be sure that you have XARELTO® available to avoid missing any doses.
- If you take too much XARELTO®, go to the nearest hospital emergency room or call your doctor right away.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF XARELTO®?

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

Call your doctor for medical advice about side effects. **You may report side effects to FDA at 1-800-FDA-1088.** You may also report side effects to Janssen Pharmaceuticals, Inc., at 1-800-JANSSEN (1-800-526-7736).

Please click here for full Prescribing Information, including Boxed Warnings, and Medication Guide.

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

About the Janssen Pharmaceutical Companies

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. Janssen Research & Development, LLC is part 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 product development and the presentation of new data and analyses 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 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 31, 2017, 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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