



NEWS RELEASE

# New Global Real-World Data from Atrial Fibrillation Studies Confirm the Safety Profile of XARELTO®

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**London, UK (September 1, 2015)** - Janssen Pharmaceuticals, Inc., and its development partner, Bayer HealthCare, today announced results from PMSS (Post-Marketing Safety Surveillance) and XANTUS (XARELTO® for Prevention of Stroke in Patients with Atrial Fibrillation), their landmark real-world studies evaluating the safety of XARELTO® in people with non-valvular atrial fibrillation (NVAF). The results found the rates and patterns of major bleeding in routine clinical practice were low (2.89 and 2.1 per 100 person-years<sup>1</sup>, respectively) and generally consistent with those observed in Phase 3 clinical research. The studies, which collectively include more than 45,000 patients from 22 countries, were presented at ESC Congress 2015.

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<sup>1</sup> Incidence rate was calculated using a person-time approach: the total number of people experiencing major bleeding divided by the number of years of all people receiving XARELTO® (expressed in 100-year increments). "Real-world research is an essential complement to clinical trials and helps inform treatment decisions, and these studies confirm the safety profile of rivaroxaban in real-world settings around the globe," said PMSS study investigator W. Frank Peacock, M.D., FACEP, Associate Chair and Research Director, Emergency Medicine, Baylor College of Medicine. "These findings show the use of rivaroxaban in day-to-day care is consistent with the safety profile observed in ROCKET AF, the landmark Phase 3 study used by regulatory authorities worldwide to approve the medicine for the prevention of stroke in patients with non-valvular atrial fibrillation."

## Global Real-World Findings in NVAF

Janssen and Bayer HealthCare initiated the PMSS and XANTUS observational studies to evaluate the real-world safety performance of XARELTO® in patients with NVAF, as part of the global development program for the medicine:



### PMSS (Post-Marketing Safety Surveillance)

PMSS is an ongoing, five-year, observational study that evaluates major bleeding in NVAf patients in the U.S. taking once-daily XARELTO® over the course of treatment. The two-year data, presented at ESC, found the rates and patterns of major bleeding were generally consistent with the Phase 3 **ROCKET AF trial**.

Of the 39,052 patients taking XARELTO® in PMSS, the incidence of major bleeding was observed at 2.89 per 100 person-years. The most common bleeding site was gastrointestinal, followed by intracranial. Fatal bleeds were uncommon, with an incidence of 0.1 per 100 person-years. Of the 7,111 patients who took XARELTO® in ROCKET AF, the incidence of major bleeding was observed at 3.6 per 100 person-years. The most common bleeding site was gastrointestinal, followed by intracranial. Fatal bleeds were uncommon, with an incidence of 0.2 per 100 person-years.

Of note, PMSS is a retrospective study with no comparator arm. Methodological differences limit the interpretation of the comparison to clinical trials.

### XANTUS (XARELTO® for Prevention of Stroke in Patients with Atrial Fibrillation)

Designed by Bayer HealthCare, XANTUS is an international, prospective, single-arm, observational study to observe the rates of major bleeding and stroke over one year for people with NVAf taking once-daily XARELTO® for stroke prevention in Europe, Canada and Israel. Also presented at ESC and simultaneously published in the **European Heart Journal**, XANTUS, like PMSS, found the rates and patterns of major bleeding in routine clinical practice to be generally consistent with Phase 3 research. Of the 6,784 patients taking XARELTO®, the incidence of major bleeding was 2.1 per 100 person-years. Fatal bleeding, critical organ bleeding and intracranial hemorrhage were uncommon, and observed in 0.2, 0.7 and 0.4 per 100 person-years, respectively. The incidence of stroke was 0.7 per 100 person-years. Like PMSS, the XANTUS study had no comparator arm. Similar studies to XANTUS (XANTUS-EL and XANAP) are ongoing in the EMEA (Europe, Middle East & Africa), Latin America and Asia-Pacific regions.

"Unmatched by any oral anticoagulant in the non-vitamin K class in its size, scope and ambition, our EXPLORER research program continues to generate important clinical evidence on the real-world safety performance of XARELTO® and its potential role in addressing additional critical medical needs," said Paul Burton, M.D., Ph.D., Vice President, Medical Affairs, Janssen. "Through our global real-world safety studies, like PMSS and XANTUS, along with our clinical trials, including ROCKET AF, X-veRT in cardioversion, VENTURE-AF in catheter ablation and PIONEER AF-PCI in percutaneous coronary intervention, we are examining the complete spectrum of anticoagulant use in patients with non-valvular atrial fibrillation."

## **Our Commitment to Atrial Fibrillation and Thrombosis Research**

The EXPLORER program is an integral part of the extensive clinical development program for XARELTO®, evaluating

its use in a broad range of cardiovascular conditions. By the time of its completion, more than 275,000 patients will have participated in the XARELTO® EXPLORER clinical development program, which includes ongoing and completed studies, independent registries and non-interventional studies.

The program is a collaborative research effort with Bayer HealthCare and is a blend of completed and ongoing studies that includes six additional indication-seeking trials. EXPLORER continues to assess the safety and efficacy of XARELTO® in high-risk patient populations, such as those with chronic heart failure, coronary artery disease, peripheral artery disease, acute coronary syndrome, embolic stroke of undetermined source, active cancer or who are medically ill. Three of the studies look at different NVAF populations:

- X-Vert was the first prospective, exploratory trial comparing the safety and efficacy of XARELTO® to vitamin K antagonists (VKA), such as warfarin, in NVAF patients undergoing cardioversion, a common procedure that uses electrical stimulation to return the heart to normal rate and rhythm. Results were presented at **ESC Congress 2014** and published last year in the **European Heart Journal**.
- VENTURE-AF was the first prospective, exploratory trial examining XARELTO® as an alternative to VKA in NVAF patients undergoing catheter ablation, a frequently used interventional procedure to remove abnormal tissue in the heart that is causing the irregular heartbeat or if cardioversion is unsuccessful. Results were published in the **European Heart Journal** in May of this year.
- PIONEER AF-PCI is an ongoing study evaluating XARELTO® in NVAF patients following percutaneous coronary intervention, also known as angioplasty, with stent placement, a common procedure used to open blocked coronary arteries and restore blood flow to the heart.

## About PMSS and XANTUS

The PMSS study was designed by Janssen in conjunction with the U.S. Department of Defense (DoD) and Health ResearchTx LLC (HRTX), and in agreement with the U.S. Food and Drug Administration (FDA) as part of a post-marketing requirement, to analyze and report major bleeding events, associated risk factors and bleeding-related clinical outcomes in NVAF patients taking XARELTO®. Researchers analyzed data from January 1, 2013, to December 31, 2014, using HRTX/DoD integrated electronic healthcare records. Major bleeding cases were ascertained using a validated Cunningham (2011) algorithm, which was generally consistent with, but not identical to, the definition of major bleeding used in clinical studies, because it relied on retrospectively identified electronic medical records.

The XANTUS study was designed by Bayer HealthCare, in agreement with the European Medicines Agency (EMA), and implemented at 311 centers across Europe, Canada and Israel. All NVAF patients who were newly started on XARELTO® were eligible. Patients had follow-up visits every three months, over the duration of one year. All adverse events (AE) were recorded as AEs or serious AEs (SAEs); SAEs were followed up until a final outcome was available. Primary outcomes, including major bleeding (ISTH definition), symptomatic thromboembolic events

(including stroke, systemic embolism and transient ischemic attack), heart attack and all-cause death, were centrally assessed. Patients were enrolled from June 2012 to December 2013.

## About XARELTO® (rivaroxaban)

XARELTO® works by blocking the blood clotting Factor Xa. XARELTO® does not require routine blood monitoring. XARELTO® has a broad indication profile and is approved for six indications that include:

To reduce the risk of strokes and blood clots in patients 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.

To treat patients with deep vein thrombosis (DVT).

To treat patients with pulmonary embolism (PE).

To reduce the risk of recurrence of DVT or PE following an initial six-month treatment for acute venous thromboembolism.

To reduce the risk of blood clots in the legs and lungs of patients who have just had knee replacement surgery.

To reduce the risk of blood clots in the legs and lungs of patients who have just had 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®)
- 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®/Eptol®)
- Phenytoin (Dilantin-125®, Dilantin®)
- Phenobarbital (Solfoton®/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®?" above.

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.

Janssen and Bayer HealthCare together are developing rivaroxaban.

For more information about XARELTO®, visit [www.xarelto-us.com](http://www.xarelto-us.com). The XARELTO® CarePath®#8482 Support Program is a resource designed for healthcare providers, patients and caregivers. Visit [www.xareltocarepath.com](http://www.xareltocarepath.com) or call 1-888-XARELTO to learn more about the XARELTO® CarePath®#8482 resources focused on access, education and adherence.

## About Janssen

At Janssen, we are dedicated to addressing and solving some of the most important unmet medical needs of our time in oncology, immunology, neuroscience, infectious diseases and vaccines, and cardiovascular and metabolic diseases. Driven by our commitment to patients, we develop innovative products, services and healthcare solutions

to help people throughout the world. Janssen Pharmaceuticals, Inc. is one of the Janssen Pharmaceutical Companies of Johnson & Johnson. Please visit [JanssenPharmaceuticalsInc.com](http://JanssenPharmaceuticalsInc.com) for more information.

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