



Janssen Research & Development Submits XARELTO® (rivaroxaban) to U.S. FDA for the Treatment and Prevention of Recurrent Venous Thromboembolism

RARITAN, May 2, 2012 - Janssen Research & Development, LLC, (Janssen), announced today that it has submitted supplemental New Drug Applications (sNDAs) to the U.S. Food and Drug Administration (FDA) seeking approval for the use of XARELTO® (rivaroxaban), an oral anticoagulant, to treat patients with deep vein thrombosis (DVT) or pulmonary embolism (PE) and prevention of recurrent venous thromboembolism (VTE).

These submissions are supported by data from the global EINSTEIN program, which included two Phase 3 studies that evaluated the safety and efficacy of rivaroxaban in the treatment of patients with acute symptomatic DVT or PE and the prevention of recurrent, symptomatic VTE in these patients. The third Phase 3 study evaluated the safety and efficacy of rivaroxaban in the long-term prevention of recurrent symptomatic VTE. In total, these Phase 3 studies included more than 9,400 patients.

DVT is a condition in which blood clots form in one of the large, deep veins, usually in the legs. PE is a serious condition that most commonly occurs when part or all of a DVT dislodges and travels to the heart, where it can partially or completely block a branch of the pulmonary artery. When PE occurs with large clots, multiple clots, or when the patient already has pre-existing heart or lung disease, the event may be fatal. VTE is the collective term for both DVT and PE. Each year an estimated 900,000 Americans experience an episode of VTE, resulting in an estimated 300,000 annual deaths.

About the EINSTEIN Program

The EINSTEIN program included three Phase 3 studies. The EINSTEIN-PE study was an open-label, randomized, non-inferiority trial. The trial compared oral rivaroxaban - 15 mg twice daily for three weeks, followed by 20 mg once daily - with the current standard of care of enoxaparin followed by a Vitamin K Antagonist (VKA) in patients with acute symptomatic PE with or without symptomatic DVT. EINSTEIN-PE enrolled 4,833 patients, who received treatment for six or 12 months of therapy, making it the largest study ever conducted in the acute treatment of PE. Results from [EINSTEIN-PE](#) were presented at the American College of Cardiology Annual Scientific Sessions, and published in the *New England Journal of Medicine* in March 2012 ([n engl j med 10.1056](#)).

The EINSTEIN-DVT study compared the safety and efficacy of oral rivaroxaban - administered at 15 mg twice daily for three weeks followed by 20 mg once daily - to standard therapy of enoxaparin followed by VKA. More than 3,400 patients with acute symptomatic DVT in the deep veins of the knee or thigh, but without any symptoms of PE, were enrolled and received treatment for three, six or 12 months of therapy. Results from [EINSTEIN-DVT](#) were presented at the annual European Society of Cardiology Congress, in August 2010.

EINSTEIN-EXT evaluated 1,197 patients who had previously completed six to 12 months of treatment with a VKA for an acute episode of VTE or had participated in the Phase 3 EINSTEIN-DVT or EINSTEIN-PE trials, in which they were treated with either rivaroxaban or a VKA. Upon enrolling in EINSTEIN-EXT, patients were randomized to receive either 20 mg of rivaroxaban dosed once-daily or placebo and were evaluated for an additional six or 12 months. Results from [EINSTEIN-EXT](#) were presented at the annual meeting of the American Society of Hematology in December 2009. Data from EINSTEIN-DVT and EINSTEIN-EXT were published together in the *New England Journal of Medicine* in December 2010 ([n engl j med 363;26](#)).

About XARELTO® (rivaroxaban)

XARELTO® belongs to a group of medicines called anticoagulants, and works by blocking the blood clotting Factor Xa, thereby reducing the tendency to form clots. In the U.S., XARELTO® is indicated to reduce the risk of blood clots in the legs and lungs of people who have just had knee or hip replacement surgery, and to reduce the risk of stroke and other complications related to migrating blood clots in people with atrial fibrillation not caused by a heart valve problem. There is limited information on how XARELTO® compares to a medicine called warfarin in reducing the risk of stroke when the blood levels of warfarin are well-controlled. The blood levels of warfarin often vary in patients.

The extensive program of clinical trials evaluating rivaroxaban makes the compound the most studied oral, Factor Xa inhibitor in the world today. Rivaroxaban is being developed jointly by Janssen Research & Development, LLC and Bayer HealthCare. U.S. marketing rights for XARELTO® are held by Janssen Pharmaceuticals, Inc.

About Janssen Research & Development, LLC

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 Research & Development, LLC and Janssen Pharmaceuticals, Inc., are part of the Janssen Pharmaceutical Companies of Johnson & Johnson. Please visit www.janssenrnd.com for more information.

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 an 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 or forming blood clots in other parts of your body.**

If you have to stop taking XARELTO®, your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.

For all people taking XARELTO®:

- XARELTO® can cause bleeding which can be serious, and rarely may lead to death. This is because XARELTO® is a blood thinner 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®)
- prasugrel (Effient®)
- ticagrelor (Brilinta®)

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:

- tingling, numbness or muscle weakness, especially in your legs. This is particularly important if you had a procedure called spinal or epidural puncture as part of your anesthesia during surgery.
- any unexpected bleeding, or bleeding that lasts a long time (such as nose bleeds that happen often, unusual bleeding from gums, or 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 (look 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

WHO SHOULD NOT TAKE XARELTO®?

Do not take XARELTO® if you:

- currently have abnormal or 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 planning to become pregnant
- Are breastfeeding or plan to 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.

- ketoconazole (Nizoral®)
- itraconazole (Onmel™, Sporan®)
- ritonavir (Norvir®)
- lopinavir/ritonavir (Kaletra®)
- indinavir (Crixivan®)
- carbamazepine (Carbatrol®, Equetro®, Tegretol®, Tegretol®-XR, Teril™, Epi®)
- phenytoin (Dilantin-125®, Dilantin®, Phenobarbital, 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.**

For people who have:

- atrial fibrillation: Take XARELTO® 1 time a day with your evening meal. Stopping XARELTO® may increase your risk of having a stroke or forming blood clots in other parts of your body.
- hip or knee replacement surgery: Take XARELTO® 1 time a day with or without food.
- 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 will have XARELTO® available to avoid missing any doses.
- If you miss a dose of XARELTO®, take it as soon as you remember on the same day.
- 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®?

XARELTO® can cause bleeding which can be serious, and rarely may lead to death. *Please see "What is the most important information I should know about XARELTO®?"*

Tell your doctor if you have any side effect that bothers you or that does not go away.

Discuss any side effects with your doctor. 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 (526-7736).

Please click [here](#) for full prescribing information, including **Boxed Warnings** and the Medication Guide.

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