

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202439Orig1s000

REMS

Initial REMS Approval: 11/2011

NDA 202,439

XARELTO® (Rivaroxaban) tablets

Factor Xa Inhibitor

Janssen Pharmaceuticals, Inc.

Titusville, NJ 08560

1-800-526-7736

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the XARELTO® REMS are:

1. To inform healthcare professionals (HCPs) that discontinuing XARELTO without introducing an adequate alternative anticoagulant places nonvalvular atrial fibrillation patients at an increased risk of thrombotic events, including stroke, and to follow recommendations in the US Prescribing Information (USPI) on how to convert nonvalvular atrial fibrillation patients from XARELTO to warfarin or other anticoagulants.
2. To inform nonvalvular atrial fibrillation patients that XARELTO should not be stopped without first informing their healthcare professional as to minimize the risks of post-discontinuation thrombotic events.
3. To inform healthcare professionals and nonvalvular atrial fibrillation patients that XARELTO (15 or 20 mg tablets) should be taken with the evening meal.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each XARELTO prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Communication Plan

Janssen Pharmaceuticals Inc. will implement a communication plan to HCPs to support the implementation of this REMS. This communication plan will include the following:

1. Dear Healthcare Professional Letter

A Dear Healthcare Professional (DHCP) Letter will be distributed by mail to: interventional cardiologists; clinical cardiologists; neurologists; emergency medicine physicians; internal medicine physicians; primary care physicians; nurse practitioners; physician assistants; pharmacists; critical care nurses, and cardiac nurse specialists. The letter will be distributed within 60 days, 12 months, and 24 months after the approval of the REMS, and in the event of any substantial safety update. A copy of the USPI and Medication Guide will accompany the DHCP Letter.

In addition, upon request, the DHCP Letter, USPI and Medication Guide will also be distributed to HCPs via sales representatives and medical science liaisons at the time of initial contact, when inquired about the risks outlined in the REMS.

The DHCP Letter is part of the REMS and is appended.

2. XARELTO REMS website

Within 30 days of REMS approval, Janssen Pharmaceuticals Inc. will post printed or web-based information for HCPs and patients on the XARELTO REMS website (www.xarelto.rems.com). This information will remain on the website for a period of 2 years.

The USPI and the Medication Guide will be provided in conjunction with the letter.

The content of the print or web-based material will include the following:

- Goals of the REMS
- Information about the risk
- Prescribing information for XARELTO
- Medication Guide for XARELTO
- DHCP Letter (for a period of 2 years)

The web-based material is part of the REMS and is appended.

3. Letters to Professional Organizations

A Professional Organization Letter will be distributed by e-mail within 60 days of the REMS approval date. This communication to professional organizations will include the same information as that contained in the DHCP Letter. Janssen Pharmaceuticals Inc. will request that these organizations disseminate this information to their members. Janssen Pharmaceuticals Inc. will communicate the letter to the leadership of the following professional organizations:

- The American Heart Association (AHA)
- The American College of Cardiologists (ACC)
- The Society for Cardiovascular Angiography and Interventions (SCAI)
- The American Academy of Neurology (AAN)
- The American Neurological Association (ANA)
- The National Institute of Neurological Disorders and Stroke (NINDS)
- The American Stroke Association (ASA)
- The National Stroke Association (NSA)
- The American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)
- The Association of Emergency Physicians (AEP)
- The American College of Chest Physicians (ACCP)
- The Association of Black Cardiologists (ABC)
- The American Academy of Family Physicians (AAFP)
- The American College of Physicians (ACP)
- The National Medical Association (NMA)
- The American Academy of Nurse Practitioners (AANP)
- The American Academy of Physician Assistants (AAPA)
- The American College of Clinical Pharmacy (ACCP)
- The American Society of Health-System Pharmacists (ASHP)

- The American Pharmacists Association (APhA)
- The American Association of Critical-Care Nurses (AACCN)
- The National Association of Clinical Nurse Specialists (NACNS)

The USPI and the Medication Guide will be provided in conjunction with the letter.

The Professional Organization Letter is part of the REMS and is appended.

C. Timetable for Submission of Assessments

Janssen Pharmaceuticals Inc. will submit REMS assessments to FDA 18 months, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Janssen Pharmaceuticals Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

IMPORTANT DRUG WARNING
XARELTO® (rivaroxaban) film-coated oral tablets

[Date]

Dear Healthcare Professional:

Janssen Pharmaceuticals, Inc. would like to inform you of important safety information for XARELTO® (rivaroxaban). XARELTO is an orally bioavailable reversible factor Xa inhibitor. XARELTO (10 mg once daily) is indicated for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery. XARELTO (15 mg and 20 mg) is now indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS), which consists of a Medication Guide and a Communication Plan, is necessary to ensure that the benefits of XARELTO outweigh the potential risks in patients with nonvalvular atrial fibrillation, including:

- Increased risk of thrombotic events, including stroke, if XARELTO is discontinued without introducing an adequate alternative anticoagulant
- Potential decreased efficacy of XARELTO (15 mg and 20 mg) if not taken with the evening meal

The XARELTO labeling includes a boxed warning to highlight the safety issue of increased risk of thrombotic events following discontinuation of XARELTO.

**WARNING: DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR
ATRIAL FIBRILLATION INCREASES RISK OF STROKE**

Discontinuing XARELTO places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following XARELTO discontinuation in clinical trials in atrial fibrillation patients. If anticoagulation with XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.

Discontinuing Administration of XARELTO in Nonvalvular Atrial Fibrillation Patients

XARELTO has a plasma half-life of 5 to 9 hours in healthy subjects (ages 20 to 45 years) and 11 to 13 hours in the elderly. Therefore, the anticoagulant effect of XARELTO is only present when

the drug is taken. Discontinuing XARELTO places nonvalvular atrial fibrillation patients at an increased risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant. Please read the recommendations in the US Prescribing Information for appropriate management of the switching or transition of XARELTO to warfarin or another anticoagulant. Additionally, advise patients to take XARELTO only as directed and not to discontinue XARELTO without first speaking to you.

Take XARELTO® (15 and 20 mg) with the Evening Meal

The 20 mg tablet has an absolute bioavailability of approximately 66% under fasting conditions, which could result in a potential risk of inadequate anticoagulation with XARELTO therapy. Coadministration of XARELTO with food can approximately increase the mean AUC by 39% and C_{max} by 76% in both the 15 mg and 20 mg strengths. XARELTO 15 mg and 20 mg tablets should be taken orally once daily with the evening meal to reduce the potential risk of decreased efficacy of therapy. Please inform your nonvalvular atrial fibrillation patients to take this medication as instructed.

Medication Guide

The Medication Guide contains information to support patient counseling regarding the risks and benefits of treatment with XARELTO. Please review the attached Medication Guide with each patient who is prescribed XARELTO. Additional copies of the XARELTO Medication Guide may be obtained from:

- the web site at www.xareltoems.com or
- the Customer Communications Center at 1-800-526-7736.

Pharmacists and other healthcare professionals who dispense XARELTO have a responsibility to provide a Medication Guide directly to each patient or caregiver with each prescription.

Reporting Adverse Events

To report any adverse events potentially associated with the use of XARELTO, contact:

- Janssen Pharmaceuticals, Inc. at to 1-800-526-7736 and/or
- FDA's MedWatch Reporting System by phone at 1-800-FDA-1088 (1-800-332-1088) or online at www.fda.gov/medwatch/report.htm

This letter is not intended as a comprehensive description of the risks associated with the use of XARELTO. Please read the enclosed US Prescribing Information and Medication Guide for a complete description of these risks.

If you have any questions about XARELTO including any information found in this letter, the US Prescribing Information and Medication Guide for XARELTO, please call our Customer Communications Center at 1-800-526-7736.

Sincerely,

Paul Chang, MD

Vice President Medical Affairs

Internal Medicine

Enclosures:

US Prescribing Information
Medication Guide

IMPORTANT DRUG WARNING
XARELTO® (rivaroxaban) film-coated oral tablets

Distribute this Information to Your Members

[Date]

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Medication Guide

The Medication Guide contains information to support patient counseling regarding the risks and benefits of treatment with XARELTO. Please review the attached Medication Guide with each patient who is prescribed XARELTO. Additional copies of the XARELTO Medication Guide may be obtained from:

- the web site at www.xareltoems.com or
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Sincerely,

Paul Chang, MD

Vice President Medical Affairs

Internal Medicine

Enclosures:

US Prescribing Information
Medication Guide

MEDICATION GUIDE
XARELTO® (zah-REL-toe)
(rivaroxaban)
Tablets

Read this Medication Guide before you start taking XARELTO and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

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®)
- 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:

- unexpected bleeding or bleeding that lasts a long time, such as:
 - nose bleeds that happen often
 - unusual bleeding from the 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

See “What are the possible side effects of XARELTO?” for more information about side effects.

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. 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.
 - reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.

It is not known if XARELTO is safe and works in children.

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 in XARELTO. See the end of this leaflet for a complete list of ingredients in XARELTO.

What should I tell my doctor before taking XARELTO?

Before you take XARELTO, tell your doctor if you:

- have ever had bleeding problems
- have liver or kidneys problems
- have any other medical condition
- are pregnant or planning to become pregnant. It is not known if XARELTO will harm your unborn baby.
- 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[™])
- 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 will decide how long you should take XARELTO. Do not stop taking XARELTO without talking with 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 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 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?

- **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.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XARELTO?

- Store XARELTO at room temperature between 59° to 86°F (15° to 30° C).

Keep XARELTO and all medicines out of the reach of children.

General information about XARELTO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XARELTO for a condition for which it was not prescribed. Do not give XARELTO to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about XARELTO. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about XARELTO that is written for health professionals.

For more information call 1-800-526-7736 or go to www.XARELTO-US.com.

What are the ingredients in XARELTO?

Active ingredient: rivaroxaban

Inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

The proprietary film coating mixture for XARELTO 10 mg tablets is Opadry® Pink contains: ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide.

The proprietary film coating mixture for XARELTO 15 mg tablets is Opadry® Red, contains: ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide.

The proprietary film coating mixture for XARELTO 20 mg tablets is Opadry® II Dark Red, contains: ferric oxide red, polyethylene glycol 3350, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

Issued: November 2011

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

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Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

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51368 Leverkusen, Germany

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