Initial REMS Approval: 11/2011

Most Recent REMS Modification: 07/2012

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 healthcare professionals that XARELTO (15 or 20 mg tablets) should be taken with the evening meal.

II. REMS ELEMENTS

A. 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.xareltorems.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.

B. 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 (November 4, 2011). 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.

The REMS assessment plan should include, but is not limited to, the following:

1. A report on the distribution of DHCP letters.

2. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with XARELTO.

3. With respect to the REMS goals, an assessment of the extent to which the REMS is meeting its goals or whether the goals or other elements should be modified.

4. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

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 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.

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]

Dear Professional Organization:

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 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.

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

Xarelto® rivaroxaban tablets

XARELTO® (rivaroxaban) Risk Evaluation and Mitigation Strategy

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

FDA has required a REMS for XARELTO® to communicate the risks of:

- 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 REMS program materials are designed to inform healthcare providers (HCPs) about the risks with XARELTO® and include a Dear Healthcare Professional Letter. It is important that you discuss with your patients the information included in the Medication Guide.

To learn more about the serious risks of XARELTO®, read the Important Safety Information provided in this link and use the links below to access REMS supporting materials:

- **Prescribing Information**
- **Dear Healthcare Professional Letter**

For additional information, please call our Customer Communications Center at 1-800-526-7736.

Last Updated: March 05, 2012 at 14:13:11 ET

IMPORTANT DRUG WARNING

XARELTO® (rivaroxaban) film-coated oral tablets

July 11, 2012

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 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.

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

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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

July 11, 20012

Dear Professional Organization:

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 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

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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.

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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.

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- 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

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Sincerely,

Paul Chang, MD

Vice President Medical Affairs

Internal Medicine

Enclosures:
US Prescribing Information
Medication Guide

Xarelto® rivaroxaban tablets

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A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

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- 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 REMS program materials are designed to inform healthcare providers (HCPs) about the risks with XARELTO® and include a Dear Healthcare Professional Letter. It is important that you discuss with your patients the information included in the Medication Guide.

To learn more about the serious risks of XARELTO®, read the Important Safety Information provided in this link and use the links below to access REMS supporting materials:

- **Prescribing Information**
- **Dear Healthcare Professional Letter**

For additional information, please call our Customer Communications Center ar 1-800-526-7736.

Last Updated: March 05, 2012 at 14:13:11 ET

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
07/12/2012