DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Roxanne McGregor-Beck, Director
Johnson & Johnson International, Inc.
1000 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

RE: NDA #202439
XARELTO (rivaroxaban) tablets
MA #215

Dear Ms. McGregor-Beck:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a direct-to-consumer (DTC) print advertisement (K02XS121040 AF) (Print Ad) for XARELTO (rivaroxaban) tablets (Xarelto) submitted by Johnson & Johnson International, Inc. (Johnson & Johnson) on behalf of Janssen Pharmaceuticals, Inc. under cover of Form FDA 2253 and observed during routine surveillance in the January/February 2013 issue of *WebMD* magazine. The Print Ad is false or misleading because it minimizes the risks associated with Xarelto and makes a misleading claim. Thus, the Print Ad misbrands Xarelto in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(n) and FDA implementing regulations. 21 CFR 202.1(e)(5)(i); (e)(7)(viii), (ix).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Xarelto.[1] According to its FDA-approved product labeling (PI), in pertinent part:

> Xarelto is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
>
> There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled.

The PI for Xarelto contains Boxed Warnings regarding increased risk of stroke after discontinuation in patients with nonvalvular atrial fibrillation and the risk of spinal/epidural hematoma. The PI also contains Contraindications regarding active pathological bleeding

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

and severe hypersensitivity reaction to Xarelto, as well as Warnings and Precautions regarding the risk of bleeding, use in patients with renal impairment and hepatic impairment, use with P-gp and strong CYP3A4 inhibitors or inducers, and risk of pregnancy related hemorrhage. The most common adverse reactions with Xarelto were bleeding complications.

Minimization of Risk Information

Promotional materials are false or misleading if they fail to present risks associated with a drug with a prominence and readability reasonably comparable with the presentation of information relating to the benefits of the drug. Factors impacting prominence and readability include typography, layout, contrast, headlines, paragraphing, white space, and other techniques apt to achieve emphasis. The Print ad prominently presents various efficacy claims for Xarelto, such as, but not limited to, the following, that are presented in large, bolded and/or colorful text and graphics (emphasis original):

- **"If you have atrial fibrillation (AFib)"**
- **"Ready to break your AFib routine?"**
- **"XARELTO® is the first and only once-a-day prescription blood thinner for patients with AFib not caused by a heart valve problem, that is proven to reduce the risk of stroke—without routine blood monitoring."**
- "…With XARELTO®, there's **no routine blood monitoring**—so you have more time for yourself. There are **no dietary restrictions**, so you're free to enjoy the healthy foods you love. And there are **no dosage adjustments**, which means you can manage your risk with **just one pill a day, taken with your evening meal**. Learn how XARELTO® can help simplify your AFib-related stroke risk treatment…."

In contrast, the risk information is presented on the preceding adjacent page without any of the emphasis (i.e. color scheme, borders, layout, and graphics) used with the efficacy claims. The result is a presentation which appears unconnected to the efficacy claims and is therefore not likely to draw readers' attention. This overall presentation misleadingly minimizes the risks associated with Xarelto because it fails to convey this important risk information with a prominence and readability reasonably comparable to the efficacy claims. We note that the Print Ad contains the statement, "**Please see accompanying Medication Guide on the following pages**" (emphasis original) at the bottom of the page, and that risk information is presented on an adjacent page, but this is not sufficient to mitigate the overall misleading presentation.

Misleading Claim

The Print Ad includes the following claim (emphasis original):

- "And there are **no dosage adjustments**…"

The above claim misleadingly suggests that dosage adjustments are not necessary with Xarelto. However, according to the DOSAGE AND ADMINISTRATION section of the PI, the dose should be lowered to 15 mg once daily for patients with renal impairment who may have a CrCL of 15 to 50 mL/min. In addition, the WARNINGS AND PRECAUTIONS section of the PI states, "…Periodically assess renal function as clinically indicated…and adjust therapy accordingly…." Thus, patients with renal impairment may need to have their dosage adjusted while on Xarelto therapy.

Conclusion and Requested Action

For the reasons discussed above, the Print Ad misbrands Xarelto in violation of the FD&C Act, 21 U.S.C. 352(n) and FDA implementing regulations. 21 CFR 202.1(e)(5)(i); (e)(7)(viii), (ix). OPDP requests that Johnson & Johnson immediately cease the dissemination of violative promotional materials for Xarelto such as those described above. Please submit a written response to this letter on or before June 20, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Xarelto that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA# 215 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official. The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Xarelto comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Amy Toscano, Pharm.D., RAC, CPA
Team Leader
Office of Prescription Drug Promotion

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

/s/

ZARNA PATEL
06/06/2013

AMY TOSCANO
06/06/2013