

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022406Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Acting Division Director
Subject	Division Director Summary Review
NDA/BLA #	22406
Supplement #	
Applicant Name	Janssen Pharmaceuticals, Inc.
Date of Submission	1/04/11
PDUFA Goal Date	7/03/11
Proprietary Name / Established (USAN) Name	Xarelto/rivaroxaban
Dosage Forms / Strength	Immediate Release Oral Tablets/10 mg film-coated
Proposed Indication(s)	For the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Min Lu, M.D./Kathy Robie-Suh, M.D./Ph.D.
Statistical Review	Qing Xu, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Yash Chopra, Ph.D./Adebayo Laninyonu, Ph.D. and Patricia Harlow, Ph.D./ Thomas Papoian, Ph.D.
CMC Review/OBP Review	Joyce Crich, Ph.D./Janice Brown, Ph.D. and Tapash Ghosh, Ph.D./Patrick Marroum, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Joseph Grillo, Ph.D./Julie Bullock, Ph.D.
DDMAC	James Dvorsky
DSI	Susan Thompson, M.D./Tejashari Purohit Sheth, M.D./Leslie Ball, M.D.
CDTL Reviews	Kathy Robie-Suh, M.D., Ph.D.
OSE/DMEPA	Denise V. Baugh, PharmD, BCPS/Carol Holquist, RPh
OSE/Epidemiology	Kate Gelperin, M.D./John Senior, M.D.
OSE/DRISK	
Other - statistical safety	John Yap, Ph.D./ LaRee Tracy, Ph.D./Aloka Chakravarty, Ph.D.
Other – Pediatrics	Elizabeth L. Durmowicz, M.D./Hari C. Sachs, M.D./Lisa Mathis, M.D.
Maternal Health Team	Dr. Upasana Bhatnagar, MD/ Karen Feibus, M.D./ Lisa Mathis, M.D.
Other- Pharmacometrics	Nitin Mehrotra, Ph.D./Christine Garnett, Ph.D.

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

Signatory Authority Review Template

1. Introduction

Xarelto is an oral Factor Xa inhibitor. Johnson and Johnson Pharmaceutical Research and Development LLC initially submitted this NDA on July 22, 2008 for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery. However the application could not be approved during the first cycle due to the need to clarify chemistry, manufacturing and control issues, need for additional understanding of potential safety issues and need for additional clarification of data integrity issues. The applicant was sent a complete response letter on May 27, 2009. The applicant responded to the complete response letter on January 4, 2011.

Xarelto has been approved by the European Medicines Agency since May 6, 2009.

2. Background

The FDA has approved four drugs for use in the prevention of venous thromboembolism (VTE) in the setting of hip and/or knee replacement surgery. All these drugs are administered parenterally (enoxaparin, fondaparinux, dalteparin and unfractionated heparin). Warfarin is the only FDA-approved oral anticoagulant approved for the prophylaxis of venous thrombosis and its extension pulmonary embolism in general. However, warfarin, is not specifically indicated for use in the prevention of VTE in the perioperative period but is widely used and numerous publications have cited use in this setting.

Unlike warfarin, rivaroxaban does not require anticoagulation parameter monitoring of the prothrombin time (PT). However, rivaroxaban does prolong the partial thromboplastin time (PT) and partial thromboplastin time (PTT). Additionally there is a linear relationship between exposure and PT prolongation. Dose dependent inhibition of Factor Xa was observed in clinical pharmacology trials.

A single dose of 10 mg daily is recommended for all patients. However, the clinical pharmacology review team recommended and continues to recommend the development of a lower strength formulation for dose modification to be used in certain populations of patients who may be more sensitive to rivaroxaban.

The original submission had four major trials submitted (RECORD 1, 2, 3, and 4) in support of the application. These trials were reviewed and the review team determined the trials supported an efficacy determination. However, during the first review cycle a number of deficiencies were identified in the areas of chemistry, manufacturing and control, clinical safety, and data integrity issues. The text in italics below is from the May 2009 complete response letter.

Chemistry Manufacturing and Control Issues

3. DMF (b) (4) is inadequate in support of this NDA.
4. DMF (b) (4) is inadequate in support of this NDA.
5. DMF (b) (4) is inadequate in support of this NDA.
6. The drug substance information is not adequate in that it does not meet 21 CFR 314.50(d)(1)(ii). Insufficient information is provided to confirm nomenclature, description, physicochemical properties, specifications, the primary stability protocol, the post-approval stability commitment and primary stability data.
7. The drug product specification, as provided by Bayer HealthCare Pharmaceuticals, Inc. is inadequate because it does not propose analytical methods for test parameters. Additionally, the proposed acceptance criteria for uniformity of dosage units do not meet the current USP requirements.
8. The proposed acceptance criteria for uniformity of dosage units and dissolution are different between Bayer HealthCare Pharmaceuticals and Janssen Ortho Pharmaceuticals. Justify this difference or alternatively, resolve the discrepancy.
9. The currently-proposed acceptance criterion for dissolution is not acceptable and is recommended to be $Q = (b) (4)$ at 15 minutes.
10. The container and closure system is not adequately described.
11. The proposed stability study is inadequate in that no stability data are submitted for pilot or commercial batches. In addition, a postapproval stability protocol and stability commitment were not submitted for Bayer Pharmaceuticals, Inc.

Data Integrity Issues

1. Investigator audits of a total of 11 clinical investigator sites, your firm as the applicant, and Bayer Pharmaceuticals as the sponsor of the "RECORD" studies (RECORD 1, 2, 3, and 4), were undertaken to evaluate the conduct of these four studies. These studies supplied most of the clinical data in support of the requested indication.

Clinical Investigator Inspections

A total of eight clinical investigator inspections by FDA, two each for the following studies, have been completed as part of the data audit for this NDA: RECORD 1, 2, 3, and 4. For the RECORD 1 study, data from the two clinical investigators audited by FDA are considered reliable in support of this NDA. For the RECORD 2 study, data from one of two clinical investigators audited by FDA are not considered reliable in support of this NDA (Dr. Qingming Yang). For the RECORD 3 study, one of two investigators audited, Dr. Bingfang Zeng, had a field classification of Official Action Indicated (OAI), indicating that serious deficiencies were noted which raised concerns regarding human subjects protection, although the data appeared acceptable for use in support of the NDA. For the RECORD 4 study, data from one of two audited clinical investigators are not considered reliable in support of this NDA (Dr. Michael Murray).

In addition to these eight clinical investigator inspections that were conducted following the NDA submission, two additional clinical investigators were inspected prior to the NDA submission as a result of complaints. These complaints pertained to the RECORD 2 study

(Dr. (b) (4) and the RECORD 4 study (Dr. (b) (4)). Based upon the inspection findings, the data from both of these sites are considered unreliable.

The data from the five sites listed above are considered unreliable for the following reasons:

- Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60].
- Failure to report adverse events to the sponsor [21 CFR 312.64].
- Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the inspection [21 CFR 312.62 (b)].
- Failure to obtain adequate informed consent [21 CFR 50]
- Failure to maintain drug accountability records [21 CFR 312.62 (a)]
- Failure to report to the IRB all unanticipated problems involving risk to human subjects [21 CFR 312.66].

Bayer Pharmaceuticals informed us of data integrity issues pertaining to an additional RECORD 4 study clinical investigator, Dr. Ricardo Esquivel in Naulcapan, Mexico. These issues included an inability to confirm that study medication was administered consistent with protocol expectations, due to a systematic discarding of medical records documenting study drug administration.

Sponsor Inspection

Inspection of Bayer Pharmaceuticals as the sponsor of the four RECORD 4 studies revealed that the sponsor failed to 1) ensure proper monitoring of the study, 2) to ensure the study was conducted in accordance with the protocol and/or investigational plan, and 3) to ensure that FDA and all investigators were promptly informed of significant new adverse effects or risks.

In order to address the issues outlined above we request that you:

a. Provide the following information regarding your clinical data quality assurance (QA) audit program that was in place for the four RECORD studies:

i. A report of your QA audit plan, including your plan for securing compliance from non-compliant clinical investigators. Include copies of any Standard Operating Procedures (SOPs) that were in place during conduct of the study to address the means by which corrective actions were to be taken if or when you or the applicable contract research organization (CRO) identified noncompliant clinical investigators.

ii. A report of your audit findings, including any corrective actions taken and final outcomes for the Yang, Murray, (b) (4), and Esquivel sites and for all other sites you audited under your QA program.

iii. A description of any clinical investigators terminated for non-compliance. Provide a list of these clinical investigators, their sites, the specific violations, and whether the data were included in the NDA submission.

b. Describe Bayer's QA program with respect to the oversight of CROs that were hired

to monitor the clinical sites, including [REDACTED] ^{(b) (4)} for the RECORD 4 study. Describe the procedures implemented to make sure that the CROs adequately monitored the clinical sites. In your response, include the following information:

- i. How was Bayer kept apprised by the CROs concerning monitoring of the clinical sites during the course of the study? Specifically, what information did the CROs provide? Provide a list of non-compliant clinical study sites reported by the CROs.
 - ii. How did Bayer review the information obtained from the CROs, during the course of the study and at the end of the study? What monitoring information was kept at the end of the study?
 - iii. What actions did Bayer take based on the monitoring reports?
- c. Provide assurance that the clinical data obtained from the RECORD 1, 2, 3, and 4 studies are reliable. Specifically, perform an additional audit and supply the results of this audit within your response to this letter. Within your response, include:
- i. A copy of your audit plan, including the following information:
 - How many clinical sites were to be audited, how many subject records were examined, and a description of the process for selection of the audited sites.
 - If not all subject records at a given clinical site were to be audited, describe how subject records were sampled and how the specific data from each subject were audited.
 - ii. The timeline for completion of your audit (plan finalization, start date, completion date, report finalization date).
 - iii. In addition to any other information within your audit report, address the following questions or requests:
 - At each site audited, how many violations involved each of the following specific issues? For each specific violation, list the clinical sites involved and provide a breakdown by treatment group for each site and overall for the four RECORD studies.
 - Enrollment of subjects that did not meet study eligibility criteria.
 - Failure of the Principal Investigator to ensure that all associates and colleagues assisting in the investigation were meeting the commitments of the study protocol.
 - Failure to report adverse events and serious adverse events
 - Failure to randomize subject preoperatively
 - Failure to obtain informed consent from all subjects
 - List all clinical sites where either Bayer or CRO monitoring is determined to be ineffective, either in identifying significant violations or in taking actions towards securing compliance (such as notifying the sponsor).

Clinical Safety Issues

2. *The supplied clinical data are insufficient to fully characterize a potential risk for serious liver toxicity. We request the following information:*

a. A report that assesses the potential signal for severe liver toxicity in your major on-going clinical studies of patients with atrial fibrillation (the "ROCKET" studies). Provide this report in a manner that does not compromise the analytical integrity of these studies. Base this report upon the findings from a data safety monitoring board's review of the clinical information for patients reported to have serum alanine aminotransferase (ALT) values greater than three times the upper limit of normal along with serum total bilirubin values greater than twice the upper limit of normal. The board's review should, at a minimum, consist of the review of all available clinical data for the index patients along with the treatment assignment. In reviewing these data, the board should consider any possible imbalance in the occurrence of the liver test abnormalities as well as each patient's clinical features, particularly those related to liver abnormalities. We welcome a discussion with you to address the most appropriate method to report the board's findings to us.

b. A report of the safety findings from the rivaroxaban post-marketing experience outside the United States. Include tabular and text summaries of spontaneously reported adverse events and an estimate of the numbers of patients exposed in the market place.

c. A report that provides a summary of post-marketing studies initiated outside the United States, to include a description of the study designs, a status update (e.g., date of initiation, numbers of enrolled subjects) as well as a summary of adverse events detected in these studies. Additionally, provide a copy of the protocol for the "observational" postmarketing study you cited at the March 19, 2009, Advisory Committee.

d. Provide a final report for the "ATLAS ACS TIMI 46" study, including electronic datasets sufficient to verify the safety and efficacy data.

Additionally in the Complete Response Letter, the sponsor was asked to address the following:

Clinical Pharmacology:

Provide a description of your plans to develop a lower strength formulation to be used for dose modification in certain special populations of patients.

Carton and Container:

Please submit draft labeling revised as follows.

a. Revise the established name on the bulk container label (30 tablets) to include the dosage form as follows: (b) (4)

b. The size of the graphic on the principal display panel is more prominent than the size of the established name and proprietary name. The proprietary name, established

name and strength should be the most prominent information on the container label and carton labeling.

c. Delete or relocate to the side panel the [REDACTED] (b) (4) statement as it crowds the principal display panel on the container label and carton labeling.

d. Provide a more specific description (e.g., color, shape, size, resin) for bottles used as containers (NDC 50458-580-30) in the How Supplied section. In addition, include the carton as a container for [REDACTED] (b) (4) blister packs, and provide a description in the How Supplied Section (section 16) of the package insert labeling.

3. CMC/Device

Drs. Crich, Brown, and Pope-Miksinski reviewed this supplement. Dr. Lostritto has also reviewed this supplement. In their reviews they state the following:

From a Chemistry, Manufacturing and Controls standpoint, this NDA is recommended for approval a 30 month shelf life for the drug product in HDPE bottles and a 18 month shelf life for the drug product in blisters, when stored at 20°-25°C (68°F - 77°F) or room temperature; excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature].

4. Nonclinical Pharmacology/Toxicology

Drs. Chopra and Laniyonu performed the first cycle review and did not identify any issues that would preclude approval. Drs. Harlow and Papoian reviewed the 2 year carcinogenicity studies in CD-1 Mice and Wistar rats. A slight increase in tumors was noted in the Wistar rats study; however, this increase was not statistically significant. The observed increase does not affect the approvability of this NDA which is for short-term use.

5. Clinical Pharmacology/Biopharmaceutics

The recommended dose is 10 mg per day with or without food. Dose modification is suggested for those who will take rivaroxaban with a strong PgP and CYP 3A4 inducer.

From the first cycle review:

Dose-dependent inhibition of FXa activity and prolongation of the prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® were observed in humans. The offset of the pharmacodynamic effect (24-48 hours) parallels the pharmacokinetic half-life. The relationship between exposure and PT prolongation appears linear.

There are no issues which would preclude approval of rivaroxaban based on the clinical pharmacology reviews. However, the clinical pharmacology review team recommends the following post-marketing commitment and requirement from their second cycle review:

Commitment

1) Develop and propose a 5 mg dosing form (tablet) or scored 10 mg tablet to allow for proper dose titration when rivaroxaban needs to be co-administered in patients at risk for clinically relevant changes in rivaroxaban exposure. The 5 mg dose form should be sufficiently distinguishable from the 10 mg tablet. Full chemistry, manufacturing and controls (CMC) information for the 5 mg dosage form including the batch data and stability data, labels, updated labeling, and updated environmental assessment section is required in a prior approval supplement.

Requirement

2) The applicant should evaluate the effect of renal impairment (i.e., mild, moderate, severe) plus the concurrent use of P-gp and moderate inhibitors of CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in volunteers so that appropriate dosing recommendations can be developed in these populations following the development of the 5 mg tablet formulation.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

I have read the first cycle clinical reviews from Drs. Rieves, Robie-Suh, and Lu. Drs. Lu's and Robie-Suh's primary concerns regarding the application were safety, not efficacy. They were concerned that insufficient safety information on hepatotoxicity was available to assess the full-risk benefit profile. Dr. Lu concluded the Executive Summary of her first cycle review by stating the following:

Overall rivaroxaban demonstrates efficacy in the prophylaxis of total VTE in patients undergoing elective hip or knee replacement surgeries.

The RECORD 1, 2, 3, and 4 trials provided the efficacy and safety database for the both indications:

- the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery and
- the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing knee replacement surgery.

All four trials were international, randomized, double-blind, double-dummy, active control (enoxaparin), parallel group design enrolling patients undergoing elective surgery for hip replacement (RECORD 1 and RECORD 2) or for knee replacement (RECORD 3 and RECORD 4).

From Dr. Lu's first cycle review:

Four multi-center, randomized controlled trials (RECORD 1-4) were conducted to support the currently proposed indication for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgeries. RECORD 1 and 2 studies were conducted in patients undergoing hip replacement surgery (THR) and RECORD 3 and 4 studies were in patients undergoing knee replacement surgery (TKR). In all 4 RECORD trials, rivaroxaban 10 mg once daily administered orally at least 6 to 8 hours after surgery was compared with enoxaparin administered subcutaneously. The enoxaparin dosing regimen was 40mg once daily starting 12 hours preoperatively in RECORD 1-3 studies and was 30 mg twice daily starting 12 to 24 hours postoperatively in RECORD 4 study. The durations of active treatment for rivaroxaban and enoxaparin were similar in the RECORD studies with the exception of RECORD 2, in which treatment duration of Rivaroxaban was much longer than enoxaparin control (rivaroxaban 35 days versus enoxaparin 13 days). The dose regimen of enoxaparin (40 mg once daily) control in RECORD 3 study is not a recommended dose regimen of enoxaparin for the prophylaxis of DVT in patients undergoing TKR in the United States.

Altogether a total of 12,729 patients (6356 in the rivaroxaban group and 6373 in the enoxaparin group) were randomized in 4 RECORD studies and 8,512 (67%) (4248 in the rivaroxaban group and 4264 in the enoxaparin group) were included in the Modified Intent to Treat (MITT) population for the primary efficacy analysis. About 30-39% of randomized patients in RECORD studies were excluded from MITT population mainly due to no adequate assessment of DVT.

The primary efficacy endpoint was a composite endpoint of total VTE consisting of any DVT (proximal and/or distal), non-fatal PE, or death from all causes at the end of treatment in all 4 RECORD studies.

The statistical analyses supporting approval from the statistical team's review are in the table below.

Table 1. Summary of Primary Efficacy Endpoint Analysis Results (Total VTE)

Study	Rivaroxaban % (n/N)	Enoxaparin % (n/N)	ARR	p-value
RECORD 1	1.1% (18/1595)	3.7% (58/1558)	2.6%	p<0.0001
RECORD 2	2.0% (17/864)	9.3% (81/869)	7.3%	p<0.0001
RECORD 3	9.6% (79/824)	18.9% (166/878)	9.3%	p<0.0001
RECORD 4	6.9% (67/965)	10.1% (97/959)	3.2%	p=0.012

ARR=Absolute Risk Reduction
Statistical Review Team table

The Division of Scientific Investigation identified some problematic sites and investigators during their inspection and assessment. Thus, the statistical review team also performed sensitivity analyses excluding the known unreliable sites. The statistical review team reanalyzed the data removing these sites where there were drug accountability and other issues. For each RECORD trial, the sensitivity analysis

using the modified ITT population demonstrates a statistically significant difference in favor of rivaroxaban for the primary endpoint. The results are provided in table 2 below.

Table 2. Summary of Primary Efficacy Endpoint Analysis Results (Total VTE) Excluding Unreliable Sites

Study	Rivaroxaban % (n/N)	Enoxaparin % (n/N)	ARR	p-value
RECORD 1	1.1% (17/1513)	3.9% (57/1473)	2.8%	p<0.0001
RECORD 2	2.1% (17/828)	8.4% (70/830)	6.3%	p<0.0001
RECORD 3	9.7% (79/813)	18.8% (164/871)	9.1%	p<0.0001
RECORD 4	7.1% (53/742)	10.8% (79/731)	3.7%	p=0.0174

ARR=Absolute Risk Reduction

Removing the problematic investigators/sites suggested that the results are still supportive of efficacy claims. However, the Agency has additional concerns regarding the study conduct and data collected in RECORD 4 which are discussed later.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstrations of efficacy for both indications.

8. Safety

During the first review cycle, the review team identified several areas for rigorous safety review: bleeding events, cardiovascular events, hepatotoxicity, and renal toxicity.

Bleeding Events:

Review of the bleeding events revealed an increase in major bleeding events for the rivaroxaban treated patients; however the difference was not statistically significant. In subgroup analyses, for Asian subjects and those subjects with body weight ≤ 50 kg or ≥ 110 kg the bleeding risk appeared to be higher for those subjects with rivaroxaban treatment.

Cardiovascular Events:

No statistically significant differences were noted between treatment groups during treatment. However, a slightly higher incidence of ischemic stroke was noted after subjects stopped rivaroxaban treatment. The significance of this increase is unclear.

Hepatotoxicity:

The clinical team's greatest concern during the first cycle review was for hepatotoxicity. The review team requested additional long term follow-up data from the ROCKET studies where rivaroxaban was used for stroke prophylaxis in patients with atrial fibrillation. In addition to the clinical and statistical review teams, two other teams analyzed the rivaroxaban safety data for hepatotoxicity: Drs. Senior and Gelperin from OSE and Drs. Yap, Tracy and Chakravarty from statistics. The longer term data did not reveal a significantly different liver toxicity profile compared with warfarin and enoxaparin.

Renal toxicity:

There were slightly higher incidences of creatinine and urea elevations in the rivaroxaban treated subjects compared with the active control subjects.

Dr. Lu concluded in her second cycle review the following:

The other adverse events reported more frequently with rivaroxaban as compared to the control were pruritus, wound healing complications, pain in extremity, increased muscle tone and cramping, wound secretion, blister, syncope, and dysuria in clinical trials. Other significant adverse events reported associated with rivaroxaban treatment in post-marketing spontaneous reports were cerebral hemorrhage, epidural hematoma, hypersensitivity reactions including anaphylactic shock, agranulocytosis, and Steven-Johnson syndrome.

I concur with the conclusions of the clinical and statistical review teams.

One of the safety issues associated with rivaroxaban use is the lack of knowledge about a method to reverse anticoagulation (including excessive anticoagulation). This information would be crucial for practicing physicians to have. The division will request from the sponsor a method to amass cases of major bleeding seen post-approval, collect information on rivaroxaban dosing, outcome of major bleeding, and any treatment for the major bleeding.

9. Advisory Committee Meeting

This product was discussed at a Cardiovascular and Renal Advisory Committee meeting on March 19, 2009. The Committee voted 15 (yes) to 2 (no) that the available clinical data demonstrate a favorable risk-benefit profile for rivaroxaban in the prophylaxis of venous thromboembolism in patients undergoing hip or knee replacement surgery.

10. Pediatrics

The applicant requested a full waiver and the pediatric review committee concurred.

11. Other Relevant Regulatory Issues

Maternal Health was consulted and provided labeling recommendations which were incorporated into labeling.

Office of Surveillance and Epidemiology was consulted including DMEPA who provided labeling input.

Division of Scientific Investigation (DSI)

As listed in section 2 above, at the conclusion of the first review cycle, DSI identified a number of items that they requested the company address based on their initial investigation and inspections. These items are listed in the May 2009 Complete Response letter. DSI has reviewed the applicant's responses to Agency requests. DSI agrees that the company did respond to all their requests and outstanding issues.

From their review, the DSI review team states that they believe the data from RECORD trials 1, 2, and 3 are reliable and that the data from RECORD 4 are not. The data integrity concerns for RECORD 4 involve the following areas:

1. Post-operative Randomization

DSI inspection discovered that some patients in the RECORD trials were post-operatively randomized to a particular treatment group. Based on the inspection, the percentage of patients was less than 1% for the RECORD trials 1, 2, and 3. However, for RECORD 4 this percentage was approximately 39%. Why the post-operative randomization was so high for RECORD 4 is not understood. When this error was discovered the company did attempt to educate the sites to randomize pre-operatively. Despite the high percentage of post-operative randomization, post-operative randomization is unlikely to have introduced any bias in favor of rivaroxaban over enoxaparin for efficacy or safety.

2. Unreported Adverse Events

All four RECORD trials had unreported adverse events. The trial with the highest number of unreported adverse events was RECORD 4. In the (b) (4) audit, RECORD 4 trial had 265 unreported adverse events. The next highest total for unreported adverse events was observed with RECORD 2 trial where there were 131 unreported adverse events. In the (b) (4) audit, RECORD 4 trial had 504 unreported adverse events.

The applicant analyzed the safety data including and excluding RECORD 4 data and the percentages for each adverse event/reaction did not change significantly.

3. Drug Accountability Issues

Drug accountability issues were identified in 27-33% of the audited sites. These issues were observed for all RECORD trials. Drug accountability issues identified by the inspection fall into different categories:

Medication return

For both treatment groups, greater or less treatment medication (tablet or injections) were returned by trial participants than would have been expected. Review of the inspection reports revealed that these types of returns occurred for both treatment arms.

Timing of Administration

Problems with record keeping for timing of administration included discrepancies in the timing of administration, who and when administered and medication given at home. These discrepancies were noted on case report forms, medical records, and as well as site logs.

4. Inadequate Monitoring

DSI inspection of Bayer did uncover problems with the monitoring of the 4 RECORD trials. An inspection of Johnson & Johnson did not uncover similar problems.

The issues uncovered during the Bayer inspection include failure 1) to ensure proper monitoring of the study, 2) to ensure the study was conducted in accordance with the investigational plan, and 3) to ensure that the FDA and all investigators were promptly informed of significant new adverse events or risks. Failure to ensure proper monitoring of the study includes the fact that Bayer's monitoring program did not detect what should have been major violations at sites. Failure to ensure that the study was conducted in accordance with the investigational plan includes the fact that 39% of RECORD 4 audited sites had post-operative randomization. Failure to ensure that the FDA and all investigators were promptly informed of significant new adverse events or risks includes the large number of unreported adverse events mentioned above for RECORD 4.

Bayer acknowledged the problems with monitoring. Also noted is the fact that Bayer did inform the FDA about problems with 2 investigators in RECORD 4: Dr. (b) (4) and Dr. Esquivel more than a year prior to submission of the NDA and one investigator in RECORD 2: Dr. (b) (4)

Based on the DSI inspection, the two inspected sites for RECORD 1 received no action indicated (NAI) letters with no recommendations for any action and the two inspected sites for RECORD 3 received voluntary action indicated (VAI) letters with recommendations for improvement. One investigator (Dr. (b) (4)) in RECORD 2 received an Official Action Indicated letter and that data was deemed not usable. Based on the DSI inspection, one site for RECORD 3 received an untitled Official Action Indicated letter and three additional sites received VAI letters with recommendations for improvement. One investigator (Dr. (b) (4)) in RECORD 4 received an Official Action Indicated and had a Notice of Initiation of Disqualification Proceedings and an Opportunity to Explain letter. Another site in RECORD 4 was deemed to have produced unusable data (Dr. Esquivel). Another site (Dr, Murray) in

RECORD 4 received an Official Action Indicated Letter. The fourth site (Dr. Fox) received a VAI letter. DSI findings are further detailed in the DSI teams' reviews.

Conclusion

While DSI had some concerns regarding each of the RECORD trials, the RECORD 4 trial had significantly more numerous and severe study conduct, oversight and data collection issues. Given the totality of concerns with RECORD 4, I concur that the RECORD 4 information appears unreliable and cannot be used for an approval decision.

In summary, rivaroxaban can be approved for both prevention of VTE in the setting of hip or knee replacement surgery. RECORD 1 and 2 trials provide the support for the use of rivaroxaban in patients undergoing hip replacement surgery. The RECORD 3 trial which demonstrated the rivaroxaban's efficacy for prevention of VTE in patients undergoing knee replacement surgery is heavily supported by the RECORD 1 and 2 trials and to an uncertain extent by the RECORD 4 trial.

There are no other unresolved relevant regulatory issues.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Approval for the prophylaxis of total VTE for patients undergoing hip surgery and patients undergoing knee surgery

- Risk Benefit Assessment

The risk benefit assessment suggests that oral rivaroxaban is effective for the prophylaxis of venous thromboembolic events in patients undergoing elective hip or knee replacement surgery. The most common side effect seen was post-operative bleeding.

- Recommendation for Post marketing Risk Management Activities
Routine post-marketing surveillance except for enhanced pharmacovigilance for major bleeding events (see commitments below)
- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC)

We have asked the applicant:

to evaluate the effect of renal impairment (i.e., mild, moderate, severe) plus the concurrent use of P-gp and moderate inhibitors of CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in volunteers

to have either a post-marketing study or enhanced pharmacovigilance plan to provide data on major bleeding events associated with rivaroxaban use, outcomes and treatment to control major bleeding to develop a 5 mg dosing form

For final versions of the PMRs and PMC see the approval letter.

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/s/

ANN T FARRELL
07/01/2011