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 # Supplement #	22406
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, PhD./Adebayo Laniyonu, Ph.D. and Patricia Harlow, PhD./ 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 Maternal Health Team Other- Pharmacometrics	Elizabeth L. Durmowicz, M.D./Hari C. Sachs, M.D./Lisa Mathis, M.D. Dr. Upasana Bhatnagar, MD/ Karen Feibus, M.D./ Lisa Mathis, M.D. 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

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