CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022406Orig1s000

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

COMPLETE RESPONSE

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your new drug application (NDA) dated July 28, 2008, received July 28, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (rivaroxaban) tablets.

We acknowledge receipt of your amendments dated August 11, October 15, November 4, 5, 21, 24, and 25, December 1,16, 18, 19, and 24, 2008; January 6, 13, 23(3), 28(2), 27, 29, and 30, February 2(2), 13, 20, 24, and 25(2), March 2, 3, 4, 6, 11(2), 18(2), 25, and 26, April 1(2), 7, 17, 24, 27, and 30(2), May 1, 5(2), 11, 18, 20(2) and 21, 2009.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

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 (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).

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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.