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APPLICATION NUMBER:

022406Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 14, 2011
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-406 (2nd review cycle)
Applicant	Johnson & Johnson
Date of Submission	December 31, 2010
PDUFA Goal Date	July 3, 2011
Proprietary Name / Established (USAN) names	Xarelto/ rivaroxaban
Dosage forms / Strength	Oral tablets, (10 mg)
Proposed Indication(s)	for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery
Recommended:	Approval, with agreed upon revisions to sponsor's proposed labeling and post-marketing commitments as indicated

1. Introduction

Patients undergoing total hip replacement surgery or total knee replacement surgery are at increased risk for venous thromboembolic events (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE). Current practice recommends anticoagulant thromboprophylaxis following these procedures. Consideration for thromboprophylaxis seeks to balance risk of VTE and risk of bleeding. Several anticoagulant drug products are currently approved and marketed in the U.S. for thromboprophylaxis in hip and/or knee replacement surgery. These include: Lovenox (enoxaparin sodium)(hip replacement and knee replacement), Arixtra (fondaparinux sodium) (hip replacement, knee replacement, and hip fracture surgery) and Fragmin (dalteparin sodium)(hip replacement). All these products are administered subcutaneously. In addition heparin sodium is labeled generally for subcutaneous administration for prophylaxis of DVT. Coumadin (warfarin sodium) administered orally is approved generally "for the prophylaxis and/or treatment of venous thrombosis and its extension and pulmonary embolism".

Xarelto (rivaroxaban) Tablets is an orally administered Factor Xa inhibitor being developed as an anticoagulant for several indications. Relevant IND applications include IND 64,892 (rivaroxaban, BAY 59-7939) for antithrombotic indications and [redacted] (b) (4) for cardiovascular indications including stroke prevention in non-valvular atrial fibrillation and use in acute coronary syndromes. In the current NDA application the sponsor is seeking initial U.S. marketing approval of rivaroxaban for the indication: "for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery". The proposed dose is 10 mg orally once daily with a treatment duration of 14 days for knee surgery and 35 days for hip surgery. Xarelto was approved for this indication in Europe and Canada in September 2008 and has been approved in some other countries also.

If approved, rivaroxaban would be the first oral anticoagulant approved in the U.S. for the indication being sought and the second oral anticoagulant approved in the U.S. for any indication since approval of warfarin in 1954. [Pradaxa (dabigatran), an orally administered antithrombin inhibitor, was approved on October 19, 2010 in the U.S. for the indication "to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation"]. Other indications for which phase 2 or 3 clinical investigations of rivaroxaban are ongoing include: for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), for thromboprophylaxis in hospitalized medically ill patients, and in patients with acute coronary syndromes (ACS). Concurrent with the current resubmission of NDA 22-406 the sponsor has submitted a separate application (NDA 202439) on January 4, 2011 (received January 6, 2011) for long-term use of rivaroxaban for the prevention of stroke and systemic embolism in patients with chronic non-valvular atrial fibrillation. That application is currently under review by the Division of Cardiovascular and Renal Products (DCRP).

2. Background

This is the second review cycle for this drug product. See my Medical Team Leader/CDTL review dated 5/27/2009 for background and summary of cycle 1 review findings. Briefly, the database consisted of four trials (the RECORD 1, 2, 3, and 4 studies), each comparing rivaroxaban to enoxaparin (different regimens) with two studies for knee surgery and two studies for hip surgery. All four studies were multinational, randomized (1:1), double-blind, double-dummy, active control (enoxaparin), parallel groups design. The studies were conducted by Bayer but the right of reference for use of the studies was transferred to Johnson & Johnson (J & J) just prior to NDA submission and J & J is the sponsor of the NDA. The efficacy findings of the first cycle review found statistically significant evidence for efficacy in all 4 studies with incidence rates for the primary efficacy endpoint ("total VTE") for the rivaroxaban and enoxaparin arms, respectively, in the studies as follows: 1.1% (18/1595) and 3.7% (58/1558) in RECORD 1; 2.0% (17/864) and 9.3% (81/869) in RECORD 2; 9.6% (79/824) and 18.9% (166/878) in RECORD 3; and 6.9% (67/965) and 10.1% (97/959) in RECORD 4. A meeting of the Cardiovascular and Renal Drugs Advisory Committee on March 19, 2009 concluded that favorable benefit-risk profile had been demonstrated for use of rivaroxaban in the prophylaxis of venous thromboembolism (VTE) in patients undergoing hip or knee replacement surgery, but voiced some concerns about the strength of the signals for hepatotoxicity and the feasibility of long-term studies to further elucidate the hepatotoxicity potential. Subsequent to the advisory committee meeting, findings of the Division of Scientific Investigations (DSI) inspections of several sites, particularly in RECORD 4, identified deficiencies with regard to compliance with study procedures, completeness in reporting of adverse events and other irregularities during the conduct of the RECORD studies raising questions about the adequacy of study monitoring by Bayer and necessitating further examination of the integrity of the studies by DSI.

On May 27, 2010 the Agency issued a Complete Response (CR) letter to Johnson & Johnson (Appendix B) citing results from the DSI clinical investigator inspections indicating that some sites may be unreliable and results from the sponsor (Bayer) inspection revealing that "the sponsor failed to 1)ensure proper monitoring of the study, 2)to ensure that 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." The sponsor was requested to provide a detailed report of their clinical quality assurance (QA) audit plan including plan for securing investigator compliance, audit findings, corrective actions including termination of investigators, oversight of CROs and Bayer handling of review information obtained from the CROs. The sponsor was asked to plan and perform an additional audit and provide a full report.

Also, in the CR letter the sponsor was informed that the supplied clinical data were insufficient to fully characterize a potential risk for serious liver toxicity. The sponsor was asked to provide additional long-term safety data from the studies of rivaroxaban in patients with atrial fibrillation (ROCKET srtudies), post-marketing experience outside the U.S., final reports for other completed long-term treatment studies and summary of post-marketing studies initiated outside the U.S.

Finallly, the CR letter included deficiencies identified by Chemistry, Manufacturing and Controls (CMC) review including problems with dissolution specifications, inadequate information about the drug substance, significant DMF deficiencies and issues regarding the proposed labels.

In the resubmission the sponsor has provided a full response to the CR letter.

3. CMC/Device

The product is an immediate release 10 mg tablet. During this review cycle upon recommendation by ONDQA Biopharmaceutics review (Tapash K. Ghosh, Ph.D., 3/23/2011) the sponsor revised the dissolution specifications and method adequately (see review by Tapash K. Ghosh, Ph.D., 5/2/2011). The CMC review completed by Joyce Z. Crich, Ph.D. (signed 6/2/2011) found the additional submitted materials and response acceptable from a CMC standpoint and recommended approval of Xarelto with 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 under specified conditions. The Office of Compliance has given an overall acceptable recommendation for the facilities and from a CMC standpoint, this NDA is recommended for approval (CMC Review #3, Janice Brown, Ph.D., 6/14/2011). There were no recommendations for Phase 4 commitments or risk management measures.

4. Nonclinical Pharmacology/Toxicology

The application was found acceptable for approval from a Non-clinical Pharmacology/Toxicology viewpoint during the first cycle. No new non-clinical data are provided in the CR submission for NDA 22-406. However, the sponsor has provided full reports of carcinogenicity studies in the NDA 202-439 application for long-term use of rivaroxaban in patients with atrial fibrillation. The non-clinical carcinogenicity studies are not required for approval of the drug for the short-term thromboprophylaxis use proposed in NDA 20-406. However, review of those studies has been completed (Patricia P. Harlow, Ph.D., 06/13/2011). Two year carcinogenicity studies were performed in CD-1 mice and Wistar rats. The review found no significant evidence of neoplasia related to rivaroxaban in either rats or mice. The Executive Carcinogenicity Assessment Committee also concluded that there were no clear drug-related neoplasms in either study. The review concluded that the results of the carcinogencity studies support approvability of rivaroxaban. Dr. Harlow's review also provided recommendations for section 13.1 of the labeling based on the results of the carcinogenicity studies.

5. Clinical Pharmacology/Biopharmaceutics

Though no Clinical Pharmacology deficiencies precluding approval were included in the CR letter, the letter did request that the sponsor provide a description of its plans to develop a lower strength formulation to be used for dose modification in certain special populations. The sponsor's response included a study synopsis and proposal to conduct a Phase 1 drug

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