CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022406Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 13, 2009
To:	Rafel (Dwaine) Rieves, M.D., Director Division of Medical Imaging and Hematology Products (DMIHP)
Through:	Solomon Iyasu, M.D., M.P.H. Director Division of Epidemiology (DEPI) Office of Surveillance and Epidemiology (OSE)
From:	Kate Gelperin, M.D., M.P.H. Medical Epidemiologist Division of Epidemiology
Subject:	Ongoing evaluation of potential severe liver injury signal in rivaroxaban clinical trials
Drug Name(s):	Rivaroxaban, BAY 59-7939
Submission Number:	NDA 22-406 submitted in July 2008
Application Type/Number:	NDA 22-406
Applicant/sponsor:	Bayer/Johnson & Johnson
OSE RCM #:	2008-2019

1 INTRODUCTION

This review follows a request from the Division of Medical Imaging and Hematology Products (DMIHP) to review and comment on a potential signal for severe drug-induced liver injury identified by the OND medical reviewer during the mid-cycle review process, and to provide relevant background information regarding previous regulatory experience with hepatotoxicity signal detection, assessment, and subsequent considerations of the balance of potential therapeutic benefit(s) versus defined hepatotoxicity risk(s).

Rivaroxaban (BAY 59-7939) is a highly selective direct factor Xa inhibitor with oral bioavailability. There are three active INDs for rivaroxaban: IND 64,892 (VTE); IND 75,931 (ACS); and IND 75,238 (A Fib). The proposed indication for the current application is prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. The proposed dose is 10 mg once daily.

2 MATERIAL REVIEWED

The following materials were considered for this review:

- Dr. Min Lu's FDA mid-cycle clinical review slides dated December 2, 2008
- Proposed package insert dated July 28, 2008
- Sponsor's laboratory datasets submitted to FDA January 22 and 30, 2009
- Cases reviewed by Sponsor's expert panel (LAP), Miami, February 17-18, 2008
- Sponsor's ISLS 6-month Safety Update dated February 2, 2008; Document No. EDMS-PSDB-9405338:2.0

3 RESULTS OF REVIEW

3.1 Overview of Clinical Program

The rivaroxaban clinical program (excerpted from Dr. Min Lu's mid-cycle review slides with cut-off date September 10, 2008) includes the following:

- **Completed studies**: N=10,600 (Rivaroxaban exposure)
  - 4 phase 3 studies (RECORD 1-4): n=6183
  - 9 phase 2 studies: n=3300 (2 VTE Tx and 3 AF)
  - 51 phase 1 studies: n=1117
- **Ongoing studies**: N=16,965 enrolled (as of September 10, 2008); N=34,236 planned
  - 5 phase 3 studies:
    - 2 VTE Tx: n=3160 enrolled, n=7500 planned
    - 2 AF: n=10,008 enrolled, n=15,200 planned
    - 1 Medically ill: n=316 enrolled, n=8000 planned
  - 1 phase 2 study: ACS n=3462 enrolled, n=3500 planned
  - 1 phase 1 study: CHF n=19 enrolled, n=36 planned

3.2 FDA Safety Concerns – Potential Severe Liver Injury

3.2.1 Safety issue identified during rivaroxaban mid-cycle review

The DMIHP medical officer's mid-cycle review identified a major concern with potential severe and/or fatal drug-induced liver injury with rivaroxaban. In the completed studies, severe liver injury (defined as a concurrent increase of total bilirubin [TBL] >2x ULN and alanine aminotransferase [ALT] >3x ULN) was observed in 14/9310 (0.15%) rivaroxaban-treated patients, and 9/7001 (0.13%) patients in comparator groups, as described in Dr Lu's review. Seven cases of severe liver injury in the RECORD studies were considered to be possibly related to rivaroxaban therapy by at least one member of the sponsor's expert panel of hepatologists.

Members of the sponsor's expert panel of hepatologists considered that some cases of severe liver injury in completed and ongoing clinical trials, including at least two deaths, were possibly related, or of uncertain relationship to rivaroxaban. As presented in the mid-cycle clinical review, at least two cases of fatal liver injury for which a possible contribution of rivaroxaban has not been ruled out occurred after fewer than 30 days of drug exposure.

3.2.2 Previous FDA experience with signal detection for severe liver injury with anticoagulant drug development for short-term versus long-term indications

Previous FDA experience with assessment of severe drug-induced liver injury due to ximelagatran, an anticoagulant drug (direct thrombin inhibitor) developed for similar indications, found no cases of severe liver injury in the short-term (orthopedic) clinical trials; however, a strong signal was subsequently identified in long-term (atrial fibrillation) trials.

After full evaluation of the signal, it was determined that 37/6948 (0.5%) ximelagatran-treated patients experienced severe liver injury versus 5/6230 (0.08%) patients randomized to warfarin (relative risk 6.6; 95% confidence interval 2.6 – 16.9). An expert causality assessment of severe liver injury cases was conducted by the sponsor, and determined that study drug may have caused or contributed to the severe liver injury in 19/6948 ximelagatran-treated patients compared to 2/6230 patients in the comparator groups (relative risk 8.5; 95% confidence interval 2.0 – 36.6).

Although a signal for severe liver injury was not detected in short-term orthopedic trials with ximelagatran, analysis of long-term data showed that initial signs of liver injury were observed within the first 30 days of ximelagatran administration for six study subjects who went on to develop severe liver injury, of which four cases were considered by the sponsor to be causally related to ximelagatran administration.

A full consideration of the balance of drug benefit(s) versus risk of severe or fatal liver injury was conducted at a public Advisory Committee meeting, which determined that potential benefits of ximelagatran did not outweigh the risks. Based on this decision, the drug was not approved in the US, and subsequently the sponsor decided to withdraw ximelagatran from marketing worldwide.

3.3 Laboratory Datasets from Ongoing Rivaroxaban Clinical Trials (blinded data)

Initial inspection of clinical laboratory datasets by Dr. Ted Guo (biostatistician) from ongoing clinical trials received from the sponsor on January 30, 2009 show the following counts of cases (numbers of patients) of potential severe liver injury in ongoing clinical trials (defined as concurrent maximum ALT >3x ULN and maximum TBL >2x ULN). Please note that there were multiple measurements over the course of the trial for each patient. The greatest values of ALT and TBL of the patient were used to determine potential severe liver injury. Missing data in ALT and TBL did not affect the values of the maximum ALT and TBL. The effect of missing data has not been investigated. Therefore, these patient counts are preliminary, and current findings could potentially be somewhat biased.

Open-label long-term EINSTEIN DVT/PE (Study #11702) – ongoing

Treatment	#Patients	Mean Rx Duration in days	# Cases potential severe liver injury in available data
BAY 59-7939	1682	150	3
ENOXAPARIN 1 mg/kg s.c. / Vitamin K-antagonist p.o.	1673	154	1

Blinded long-term ROCKET-AF (Study #11630; comparator warfarin) – ongoing

Treatment labeled as	#Patients	Mean Rx Duration in days	# Cases potential severe liver injury in available data
Dummy A (BLINDED)	5495	233	8
Dummy B (BLINDED)	5492	229	12

Blinded long-term J-ROCKET-AF (Study #12620; comparator warfarin) – ongoing

Treatment labeled as	#Patients	Mean Rx Duration in days	# Cases potential severe liver injury in available data
BLINDED	1185	201	3

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.