

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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**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

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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

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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

4 DISCUSSION

Instances in clinical trials (even very few of them) of transaminase elevation accompanied by elevated bilirubin (in the absence of biliary obstruction), have been associated with, and have often predicted, post-marketing serious liver injuries (fatal or requiring transplant). Drug-induced hepatocellular jaundice is considered a serious lesion, with an estimated mortality of at least 10%. The reason is that hepatocellular injury great enough to interfere with bilirubin excretion involves a large fraction of the liver cell mass.

An FDA Office of Drug Safety review which was included in the background package for the ximelagatran Advisory Committee meeting in September 2004 is included for reference as an appendix to this memo.

5 RECOMMENDATIONS

A potential signal for severe liver injury associated with rivaroxaban therapy has not been fully characterized at this time. Complete risk assessment, fully evaluating safety data from long term clinical trials, should be undertaken in order to inform decisions about the balance of therapeutic benefit versus risk with rivaroxaban.

APPENDIX

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APPENDIX—DRUG-INDUCED LIVER INJURY

A. Brief regulatory history: withdrawals and risk management

During the past ten years, two drugs, DURACT (bromfenac) and REZULIN (troglitazone), have been withdrawn from marketing in the US because they were associated with an unacceptable risk of severe drug-induced liver injury (DILI) in the absence of a clear counter-balancing benefit. In both cases, attempts were made to manage the risk of hepatotoxicity while keeping the drug available for therapeutic use. In the case of bromfenac, approved by FDA in 1997 for use as a short-term analgesic (ten days or less), severe DILI was generally observed only in patients who took the drug for more than 30 days;⁴⁷ however, despite attempts to regulate the duration of therapy by clear statements in product labeling, prescribers did not adequately heed this information and more than 50 cases of severe DILI were reported, prompting market withdrawal in 1998. In the case of troglitazone, approved by FDA in 1997 for glucose control in patients with type 2 diabetes, reports of fatal liver injury received by FDA shortly after marketing prompted a black box warning and a series of Dear Healthcare Professional letters recommending monthly transaminase monitoring. Despite these measures, transaminase monitoring was not regularly performed.⁴⁸ Moreover, in some patients, liver injury still progressed to fatal liver failure despite stopping the drug in response to monthly transaminase monitoring due to rapid progression of liver injury to a state of irreversibility.⁴⁹ Troglitazone was withdrawn from the US market in March 2000, after 94 cases of drug-induced liver failure had been reported, most of which were fatal. A more complete discussion of troglitazone is provided in Section D of this Appendix, under the heading Specific Examples.

Also during the past ten years, there have been instances where regulatory action prompted by concern about severe DILI included risk management actions which stopped short of market withdrawal. Examples include CYLERT (pemoline) and TROVAN (trovafloxacin).

Pemoline was approved by FDA in 1975 for ADHD with recommendations in the Precautions section to monitor transaminase levels periodically due to a 1% to 2% incidence of drug-induced liver injury. Reports of acute liver failure (ALF) led to a series of black box warnings and Dear Healthcare Professional letters in 1996 and 1999, shifting the drug to second line therapy and recommending baseline and bi-weekly transaminase monitoring. Although compliance with these recommendations was assessed to be poor,⁵⁰ the use of pemoline dropped off substantially over the next five years,⁵¹ and no additional drug-related cases of liver failure were subsequently reported to FDA.⁵²

⁴⁷ Fontana RJ, McCashland TM, Benner KG, et al. Acute liver failure associated with prolonged use of bromfenac leading to liver transplantation. *Liver Transpl Surg* 1995;5:480-4.

⁴⁸ Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess M. Liver enzyme monitoring in patients treated with troglitazone. *JAMA* 2001;286:831-33.

⁴⁹ Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. *Am J Med* 2003;114:299-306.

⁵⁰ Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A study of compliance with FDA recommendations for pemoline (Cylert). *J Am Acad Child Adolesc Psychiatry* 2002, 41(7):785-790.

⁵¹ FDA/CDER/ODS/DSRCS Review of the Proposed Risk Management Communication Plan for Cylert (pemoline) dated January 16, 2004.

⁵² Racoosin JA. FDA/CDER/Division of Neuropharmacological Drug Products (HFD-120) memorandum to Patient Information Sub-Committee Members, dated February 6, 2004.

Trovafloxacin (a fluoroquinolone antibiotic) received FDA approval in 1997. During the first two years of marketing in the US, there were over 100 cases of clinically symptomatic liver toxicity, including 14 cases of ALF. An analysis of drug utilization based on data from IMS Health, National Disease and Therapeutic Index™ (NDTI™)⁵³ showed that during the period from 1998 to 1999, approximately 91% of trovafloxacin prescriptions were for five days or longer, with only about 5% of prescriptions for 20 days or longer.⁵⁴ A lag was noted between completion of trovafloxacin therapy and onset of liver symptoms in six of 14 probable ALF cases, which ranged from five to 20 days.⁵⁵ Survival analysis was conducted on the spontaneous reports, and showed that the relative risk of ALF with trovafloxacin was elevated from the start of therapy, and increased with increasing duration of exposure.⁵⁶ A Public Health Advisory in 1999 warned about severe hepatotoxicity, restricted use to certain very severe infections, and announced that the manufacturer would restrict trovafloxacin distribution to inpatient facilities only.⁵⁷

Examples of drugs never marketed in the US because of hepatotoxicity include ibufenac, perhexilene, dilevalol (a beta blocker), tasosartan (an angiotensin II receptor antagonist), and Fialuridine (FIAU).⁵⁸ In the case of dilevalol, the application was refused in 1990 based on findings of >3x ULN transaminase elevations and modest bilirubin elevation (>2 mg/dL) in a few patients, accompanied by an increased incidence of 3-fold transaminase elevation compared to placebo.⁵⁹

B. Range of issues: timing, tempo and reversibility of hepatotoxicity

Drug-induced liver injury is an important cause of fulminant liver failure. The Acute Liver Failure Study Group found that, between 1998 and 2000, 52% of all cases of ALF in the United States were due to drug-induced liver injury.⁶⁰

Drug-induced liver disease can be predictable (dose-related, occurring at doses exceeding recommendations) or unpredictable (idiosyncratic, and occurring in susceptible individuals at usual therapeutic doses).⁶¹ Idiosyncratic liver injuries occur with a pattern that is consistent for each drug and for each drug class.⁶²

⁵³ IMS Health, National Disease and Therapeutic Index, 1998-March 1999, extracted 6/99.

⁵⁴ FDA/CDER/OPDRA/DDRE Review of Trovan® (trovafloxacin and alatrofloxacin) and acute liver failure, dated July 12, 1999.

⁵⁵ *ibid.*

⁵⁶ *ibid.*

⁵⁷ Public Health Advisory (1999) Trovan (trovafloxacin / alatrofloxacin mesylate) and risk of liver failure. FDA June 9, 1999. Available from: <http://www.fda.gov/cder/news/trovan/trovan-advisory.htm>

⁵⁸ Center for Drug Evaluation and Research (CDER). Drug-induced liver toxicity. Clinical White Paper. November 2000. (Accessed June 1, 2004, at <http://www.fda.gov/cder/livertox/default.htm>.)

⁵⁹ *ibid.*

⁶⁰ Ramkumar D, LaBrecque DR. Drug-induced liver disease and environmental toxins. In: Hepatology A Textbook of Liver Disease. Fourth Edition. Zakim D and Boyer TD, (Eds.) Saunders, Philadelphia, 2003.

⁶¹ *ibid.*

⁶² Lee WM. Drug-induced hepatotoxicity. *N Engl J Med* 2003;349:474-85.

As Lee has proposed in a recent review of drug-induced liver injury,⁶³ most idiosyncratic drug reactions result from a succession of unlikely events, a “multihit” process. This implies that a “series of events that first involve intracellular disruption, cell necrosis, or apoptosis, followed by activation of the immune sequence, might explain the features of idiosyncratic drugs reactions: their rarity, their severity, and their resolution despite continued use of the drugs by patients with phenotypes that appear to be adaptive.”⁶⁴

Timing: Risk vs. duration of treatment (hazard rate over time)

Idiosyncratic reactions are characterized by a variable delay or latency period, typically ranging from 5 to 90 days from the initial ingestion of the drug, and are frequently fatal if the drug is continued once the reaction has begun.⁶⁵ The relationship of onset of liver injury with duration of drug exposure is not predictable. An increased risk of severe DILI has been found to be positively associated with increasing duration of therapy for several drugs including trovafloxacin,⁶⁶ troglitazone,⁶⁷ pemoline,⁶⁸ and bromfenac.⁶⁹

Tempo and reversibility of injury

The range of tempos of injury is a characteristic both of individual drugs and patients. Rapid acceleration of liver injury in some individuals may preclude an absolute protective value of standardized periodic transaminase monitoring.⁷⁰

A key issue in effective intervention to prevent fatal liver injury is “recoverability” at time of sign or symptom onset. This refers to a “point of irreversibility”, after which there is an inexorable progression to liver failure and often death. The contrast between isoniazid liver injury (chronic parenchymal injury)⁷¹ and that characteristic of troglitazone⁷² demonstrates the contrast between a situation where stopping the drug at the time of symptom onset most often prevents progression to irreversible injury, and one where it does not in many cases. Drugs that can cause severe DILI generally demonstrate a range of responses, with varying proportions of patients who recover whether or not the drug is stopped, versus the proportion of patients who go on to develop irreversible injury.

⁶³ *ibid.*

⁶⁴ *ibid.*

⁶⁵ *ibid.*

⁶⁶ Graham DJ, Ahmad SR, Piazza-Hepp T. (2002) Spontaneous reporting – USA. In: Mann RD and Andrews EB, (eds), *Pharmacovigilance*, John Wiley and Sons, Ltd.

⁶⁷ Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. *Am J Med* 2003;114:299-306.

⁶⁸ Safer DJ, Zito JM, Gardner JE. Pemoline hepatotoxicity and postmarketing surveillance. *J Am Acad Child Adolesc Psychiatry*. 2001 Jun;40(6):622-9.

⁶⁹ Fontana RJ, McCashland TM, Benner KG, et al. Acute liver failure associated with prolonged use of bromfenac leading to liver transplantation. *Liver Transpl Surg* 1995;5:480-4.

⁷⁰ Avigan M. Responses to a signal of drug-induced hepatotoxicity. FDA/CDER/ODS/DDRE presentation at Drug-Induced Hepatotoxicity Workshop, January 28, 2003, Washington, DC.

⁷¹ Ramkumar D, LaBrecque DR. 2003. *op cit.*

⁷² Graham DJ, Green L, Senior JR, Nourjah P. 2003. *op cit.*

Dose-related hepatotoxicity

Acetaminophen is an example of a drug with predictable dose-related toxic effects. At higher doses, acetaminophen can rapidly cause hepatocyte injury. Acetaminophen toxicity produces the most common form or cause of ALF in the US, accounting for 39% of cases in a recent survey of tertiary care centers,⁷³ both after attempted suicide by acetaminophen overdose and after unintentional overdose, in which use of the drug for pain relief in excess of the recommended dose has occurred over a period of days.⁷⁴

C. Experience with clinical trial data

Possible “signals” for severe DILI are abnormalities (signs or symptoms) that reflect ongoing liver injury 1) in the same individual if drug is continued, and 2) in other drug-treated individuals due to a common mechanism of toxicity.⁷⁵ Signals can be generated in clinical trials by subjects with clinically mild reversible drug-induced liver injury.

The observation that “instances (even very few of them) of transaminase elevation accompanied by elevated bilirubin (even if obvious jaundice was not present) have been associated with, and have often predicted, post-marketing serious liver injuries (fatal or requiring transplant)” was first made by Dr. Hyman Zimmerman,⁷⁶ and has been dubbed “Hy’s Law”.⁷⁷ The ominous implications of Hy’s Law proved to be true for bromfenac, dilevalol, troglitazone, and trovafloxacin, even though no cases of life-threatening serious injury were seen for any of these drugs pre-marketing.⁷⁸

Zimmerman noted that drug-induced hepatocellular jaundice is a serious lesion, with mortality ranging from 10 to 50 percent.⁷⁹ More recent mortality estimates continue to regard the combination of pure hepatocellular injury and jaundice as ominous, with about 10-15% of patients who show such findings as a result of drug-induced injury going on to die⁸⁰. The explanation for this outcome is that hepatocellular injury great enough to interfere with bilirubin excretion must involve a large fraction of the liver cell mass.⁸¹

Increased transaminases alone – examples

Clinical trials with statins have generally shown an imbalance in transaminase elevations (ALT >3x ULN) between active drug and placebo. However, extensive marketed experience with the

⁷³ Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care center in the United States. *Ann Intern Med* 2002;137:947-54.

⁷⁴ Lee WM. 2003. *op cit*.

⁷⁵ Avigan M. 2003. *op cit*.

⁷⁶ Center for Drug Evaluation and Research (CDER). Drug-induced liver toxicity. Clinical White Paper. November 2000. (Accessed June 1, 2004, at <http://www.fda.gov/cder/livertox/default.htm>.)

⁷⁷ Reuben A. Hy’s Law. *Hepatology* 2004 Feb;39(2):574-8.

⁷⁸ CDER. Drug-induced liver toxicity. 2000. *op cit*.

⁷⁹ Zimmerman HJ. Drug-induced liver disease. In: Hepatotoxicity The Adverse Effects of Drugs and Other Chemicals on the Liver. Appleton-Century-Crofts, New York, 1978, 1999.

⁸⁰ CDER. Drug-induced liver toxicity. 2000. *op cit*.

⁸¹ *ibid*.

older statins (e.g., simvastatin), as well as several large morbidity and mortality trials⁸², have shown that serious liver injury occurs rarely, not exceeding background, with several of these drugs. For instance, during clinical trials with lovastatin, ALT > 3x ULN occurred in 2.6% and 5.0% of patients on doses of 20 mg and 80 mg/day, respectively. The elevations are reversible with continuing therapy and are dose related. Postmarketing, lovastatin exposure is estimated worldwide to be 24 million patient-years. Rare cases of liver failure have been reported at a rate of approximately 1/1.14 million patient years, which is approximately equal to the background rate of idiopathic ALF.⁸³

Increased Hy's cases – examples

Troglitazone is an example where “Hy's cases” observed during clinical trials portended a significant postmarketing issue with severe DILI and fatal liver failure. Troglitazone is discussed below in Section D.

D. Specific Examples – long-term indications (chronic therapy)

Troglitazone

In the clinical trials which led to troglitazone's approval by the FDA in 1997,⁸⁴ there were no cases of liver failure in 2510 patients. In the NDA database (N=2510), 1.9% of troglitazone-treated patients had ALT >3x ULN, 1.7% had ALT >5x ULN, and 0.2% (5 patients) had ALT >30x ULN (two of whom also experienced jaundice). The median duration of troglitazone therapy before peak ALT elevation was 121 days. In 1997, NIH sponsored a large Diabetes Prevention Program⁸⁵ designed to determine whether non-insulin-dependent diabetes mellitus can be prevented or delayed in persons with impaired glucose tolerance. Study groups included intensive lifestyle intervention with diet and exercise, metformin or troglitazone with standard diet and exercise, and a control group. The troglitazone arm was discontinued in 1998 due to reports of severe hepatotoxicity.⁸⁶ In the NIH Diabetes Prevention Trial (N=585), 3.0% of troglitazone-treated subjects had ALT >3x ULN, 1.5% had ALT >8x ULN, and two patients had ALT >30x ULN. One of these patients developed liver failure and died, despite receiving a liver transplant. The second patient recovered. The median duration of troglitazone therapy before initial ALT elevation was 126 days, and to peak elevation was 143 days.⁸⁷

In response to worrisome and continuing reports of ALF associated with troglitazone use, a series of “Dear Healthcare Professional” letters were sent to practicing physicians between 1997

⁸² Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;360:7-22.

⁸³ Tolman K. The liver and lovastatin. *Am J Cardiol* 2002;89:1374-1380.

⁸⁴ FDA Center for Drug Evaluation and Research. Medical review of troglitazone – efficacy supplement, NDA 20-720, Dr. Robert Misbin, March 12, 1999. www.fda.gov/cder/foi/nda/99/20720S12S14_Rezulim.htm (accessed July 12, 2004).

⁸⁵ Muniyappa R, El-Atat F, Aneja A, McFarlane SI. The diabetes prevention program. *Current Diabetes Reports* 2003 Jun; 3(3):221-2.

⁸⁶ *ibid.*

⁸⁷ FDA Center for Drug Evaluation and Research. Medical review of troglitazone – efficacy supplement, NDA 20-720, Dr. Robert Misbin, March 12, 1999. www.fda.gov/cder/foi/nda/99/20720S12S14_Rezulim.htm (accessed July 12, 2004).

and 1999, warning about severe liver injury and recommending monthly transaminase monitoring. Unfortunately, transaminase monitoring was not regularly performed.⁸⁸ Moreover, an analysis of 94 cases of liver failure which were reported spontaneously to the FDA showed that the progression from normal hepatic functioning to irreversible liver injury occurred within one month in 19 patients who were indistinguishable clinically from the 70 patients who had an unknown time course to irreversibility. Of the 89 cases of ALF, only 11 (13%) recovered without liver transplantation. The onset of injury began from three days to after more than two years of troglitazone use. Progression from jaundice to hepatic encephalopathy, liver transplantation, or death was rapid, averaging 24 days. The authors concluded that “progression to irreversible liver injury probably occurred within a one-month interval in most patients, casting doubt on the value of monthly monitoring” of serum transaminase levels as a means of preventing severe DILI.⁸⁹

A marked increase in risk with each month of troglitazone use was demonstrated by Graham⁹⁰ in an analysis of interval-specific hazard rates (per million person-years) for each month of continued troglitazone use, based on ALF cases reported to the FDA (numerator) and the estimated person-years of troglitazone exposure for that corresponding month of use (denominator). A table in that report is reproduced below,⁹¹ and shows the cumulative risk of ALF calculated as “1-survival probability” for each month of continued use, derived from the life-table analysis, and expressed in the form of “1 case per x persons treated” for each month of continued use (slide 29 in the original document).

This analysis of troglitazone data through the close of 1999 showed that the interval-specific hazard rate was substantially elevated above the expected background rate of one per million person-years beginning with the first month of troglitazone use. The cumulative risk of ALF increased from one case per 131,000 users at one month of use to one case per 7,000 users with 18 months of continued troglitazone use.⁹²

⁸⁸ Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess M. Liver enzyme monitoring in patients treated with troglitazone. *JAMA* 2001;286:831-833.

⁸⁹ Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. *Am J Med* 2003;114:299-306.

⁹⁰ Graham DJ, Green L. Final Report: Liver Failure Risk with Troglitazone (Rezulin). FDA/CDER/ODS/DDRE consult, dated December 19, 2000.

⁹¹ *ibid*, page 20.

⁹² *ibid*, page 20.

Interval-Specific Hazard Rates (x10⁻⁶ pyrs) and Cumulative Risk of
Liver Failure with Rezulin, by Duration of Use*

Mon hs Use	Cases	Int Hazard	Cum Risk
			(1 per "x")
1	9	89	131K
2	5	58	79K
3	9	117	44K
4	14	206	25K
5	13	216	17K
6	8	149	14K
7	3	62	13K
8	10	230	10K
9	2	52	10K
10	2	57	9K
11	2	64	9K
12	2	72	9K
13	1	40	8K
14			
15			
16			
17	2	135	8K
18	1	79	7K

*Duration missing
for 11 cases

29

Table reproduced from Graham DJ, Green L. Final Report: Liver Failure Risk with Troglitazone (Rezulin). FDA/CDER/ODS/DDRE consult, dated December 19, 2000.

More recently, the incidence of hospitalized idiopathic acute liver injury and ALF in troglitazone-treated patients was estimated in an observational retrospective cohort study using claims data from a large multistate health care organization.⁹³ The inception cohort included 7568 patients who began troglitazone during the study period. A total of 4020 person-years of exposure were observed. The incidence rates per million person-years of acute idiopathic liver injury (95% CI) were as follows: hospitalization with jaundice (n=4), 995 per million person-years (271, 2546); ALF (n=1), 240 per million person-years (6.3, 1385). This represents a marked increase in risk compared to estimated background rates of hospitalization for idiopathic acute liver injury (22 per million person-years) and ALF (1 per million person-years).⁹⁴

Although the pathogenesis of troglitazone toxicity is not understood,⁹⁵ experience with troglitazone provides a clear example of a situation where “Hy’s Law” cases observed during clinical trials prior to approval were predictive of a high risk of severe DILI and ALF post marketing. Troglitazone was withdrawn from the US market in March 2000, after 94 cases of drug-induced liver failure had been reported.⁹⁶

⁹³ Graham DJ, Drinkard CR, Shatin D. Incidence of idiopathic acute liver failure and hospitalized liver injury in patients treated with troglitazone. *Am J Gastroenterol* 2003;98(1):175-9.

⁹⁴ *ibid.*

⁹⁵ Lee WM. 2003. *op cit.*

⁹⁶ Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. *Am J Med* 2003;114:299-306.

Isoniazid

Isoniazid remains a first-line agent against tuberculosis, even though increased levels of aminotransferase are observed in 15 to 30 percent of patients who take the medication and one in 1000 patients will have severe hepatic necrosis.^{97 98} Recent experience in public health clinics has shown that risk of severe hepatotoxic reactions to isoniazid can be effectively minimized by instructing patients to stop drug and immediately report symptoms of liver injury as soon as they occur.⁹⁹ In a recent 7-year survey from a public health tuberculosis clinic in Seattle, WA, a total of 11,141 consecutive patients who started a regimen of isoniazid preventive therapy for latent TB infection were followed to determine the rate of developing signs and symptoms of hepatotoxicity during clinically monitored therapy.¹⁰⁰ Monitoring for the safety of isoniazid was done by a clinical evaluation for symptoms rather than by transaminase monitoring because many patients experience a transient rise in serum transaminase levels during isoniazid therapy. During the 7-year study period, eleven patients (0.1%) experienced hepatotoxic reactions while receiving isoniazid. All eleven patients had highly elevated serum transaminase levels and nine (82%) patients were hyperbilirubinemic. Only one patient was hospitalized because of hepatotoxicity. All eleven patients recovered without sequelae.

Similar experience was reported from a tuberculosis clinic in California, with outcomes available for 3,788 patients started on isoniazid between 1999 and 2002. Ten patients (0.3%) developed isoniazid-associated liver injury, none of whom required hospitalization or died. The authors conclude that clinical evaluation as the primary monitoring method for most patients taking isoniazid is effective. High rates of asymptomatic transaminase elevations in isoniazid-treated patients limit the utility of routine periodic monitoring in detecting clinically meaningful liver injury that will progress to irreversibility.¹⁰¹

Pemoline

Pemoline (Cylert®), a drug for the treatment of ADHD, was approved by the FDA in 1975 as a Schedule IV stimulant. At the time of approval, hepatic enzyme abnormalities were noted in 1% to 2% of patients, leading to recommendations in the precautions section to monitor transaminase levels periodically. Postmarketing, cases of liver injury, including ALF, were reported. An analysis of 13 cases of fulminant liver failure in children treated with pemoline which had been reported to the FDA prior to 1996 found that the median duration of pemoline use prior to symptomatic liver disease was about 13 months, with the shortest duration among the 13 cases being six months.¹⁰²

⁹⁷ Lee WM. 2003. *op cit*.

⁹⁸ Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999;281:1014-18.

⁹⁹ *ibid*.

¹⁰⁰ *ibid*.

¹⁰¹ LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. *Am J Respir Crit Care Med* 2003;168:443-7.

¹⁰² FDA/CDER/Epidemiology Branch. Report on Fulminant Hepatic Failure with Pemoline (Cylert), dated April 17, 1996.

These reports of serious DILI and ALF prompted a labeling change in 1996 (black box warning) and a Dear Healthcare Professional letter, shifting the drug from first-line to second-line therapy for ADHD. In June 1999 another labeling change and Dear HCP letter was issued, with new recommendations for baseline and bi-weekly transaminase monitoring. Compliance with labeling recommendations was subsequently assessed, and was found to be poor in a retrospective cohort study using administrative claims data.¹⁰³ Recently, use of this drug has dropped sharply since there are several therapeutic alternatives. A search of the AERS safety database (covering the period from June 1999 through January 2004) indicates that no unconfounded cases of liver failure associated with pemoline therapy administered after June 1999 have been received by the FDA.¹⁰⁴ An analysis of drug utilization^{105,106} shows that the use of the drug (brand and generic) has decreased substantially over the last six years such that domestic use in 2003 (171,000 prescriptions) was about 22% of its use in 1998 (773,000 prescriptions).

E. Specific Examples – short- or intermediate-term indications

Bromfenac

Bromfenac (Duract®) was approved by FDA in 1997 for use as a short-term analgesic for periods of 10 days or less. Although no cases of serious liver injury were seen in clinical trials, the product was approved only for short term use because a higher incidence of transaminase elevations were observed in patients treated long-term in clinical trials. Bromfenac was never approved as a treatment for chronic conditions such as osteoarthritis or rheumatoid arthritis.¹⁰⁷ However, when used off label in such patients, need for chronic pain relief increased the risk of longer term use, despite precautions in the label.

During clinical trials, bromfenac use was associated with transaminase elevations in approximately 15% of patients, and elevations >3x ULN were seen in 2.7% of patients at some time during treatment. In contrast, the incidence of such elevations was <0.4% during short-term therapy. In longer term trials, marked elevations more than 8x ULN occurred in 0.4% of patients.¹⁰⁸

Post-approval, reports of hepatic failure, including four deaths and eight cases requiring liver transplant, were received. All but one of these cases involved the use of bromfenac for more than ten days, the maximum recommended duration of treatment. In response to the reports, FDA and the company strengthened the warnings in the US package insert (USPI) with a black box warning, and the company issued a Dear HCP letter. Despite these efforts, the FDA and the

¹⁰³ Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A study of compliance with FDA recommendations for pemoline (Cylert). *J Am Acad Child Adolesc Psychiatry* 2002, 41(7):785-790.

¹⁰⁴ Racoosin JA. FDA/CDER/Division of Neuropharmacological Drug Products (HFD-120) memorandum to Patient Information Sub-Committee Members, dated February 6, 2004

¹⁰⁵ FDA/CDER/ODS/DSRCS. Update to ODS/DSRCS Review of the Proposed Risk Management Communication Plan for Cylert® (pemoline), NDAs 16-832 and 17-703, dated January 16, 2004.

¹⁰⁶ Data source - IMS Health, National Prescription Audit Plus™, 1997-2003, extracted 1/04.

¹⁰⁷ FDA Talk Paper. Wyeth-Ayerst Laboratories announces the withdrawal of Duract from the market. Available from: <http://www.fda.gov/bbs/topics/ANSWERS/ANS00879.html>.

¹⁰⁸ Product Information: Duract®, bromfenac. Wyeth Laboratories, Philadelphia, PA, 1998.

company continued to receive reports of severe injuries and death with long-term use of bromfenac.¹⁰⁹

Four patients with severe bromfenac hepatotoxicity were identified at three tertiary care centers participating in the US Acute Liver Failure Study Group. Bromfenac had been administered for a minimum of 90 days at usual dosages to four women who presented with severe, symptomatic hepatocellular injury with associated hypoprothrombinemia. Despite supportive measures, all the subjects developed progressive liver failure over 5 to 37 days, leading to liver transplantation in three patients and death in one patient while awaiting transplantation. The authors concluded that the “poor outcomes in this series, coupled with the inability to identify individuals at risk for severe, idiosyncratic bromfenac hepatotoxicity preclude further use of bromfenac in the medical community.”¹¹⁰

Given the availability of other therapies, in 1998 FDA and the company concluded that it would not be practical to implement the restrictions necessary to ensure the safe use (less than ten days) of bromfenac, and that the drug should be withdrawn from the market.¹¹¹

Analysis of drug utilization during the two years prior to bromfenac’s withdrawal from the market (1997-1998), shows that 55-60% of bromfenac mentions in outpatient office visits were for intended therapy of 10 days or less, based on information from an IMS Health, National Disease and Therapeutic Index (NDTI™)¹¹², which reflects the intention of the physician at the time of prescribing. Approximately 10-20% of mentions were for more than 10 days of intended treatment and 25-30% had “unspecified” intended duration, suggesting that an even higher percentage of mentions could have been for more than 10 days of intended treatment. Among those physicians mentioning bromfenac during an office-based visit, the intended duration of therapy ranged from one to 90 days, with the most mentions occurring for 10 days of therapy (approximately 21%).¹¹³

Trovafloxacin

Following the marketing of trovafloxacin (a fluoroquinolone antibiotic) in 1998, FDA began receiving reports of patients with serious liver reactions.¹¹⁴ During pre-marketing clinical trials with trovafloxacin (N = 7000), there were no reports of liver failure. Post-marketing, FDA received reports of over 100 cases of clinically symptomatic liver toxicity, including 14 cases of ALF, many of which were fatal and/or required liver transplant. Trovafloxacin-associated liver

¹⁰⁹ FDA Risk Intervention Examples. Appendix G. Available from: <http://www.fda.gov/oc/tfrm/AppendixG.html>.

¹¹⁰ Fontana RJ, McCashland TM, Benner KG, et al. Acute liver failure associated with prolonged use of bromfenac leading to liver transplantation. The Acute Liver Failure Study Group. *Liver Transpl Surg* 1999;5:480-4.

¹¹¹ FDA Talk Paper. Wyeth-Ayerst Laboratories announces the withdrawal of Duract from the market. Available from: <http://www.fda.gov/bbs/topics/ANSWERS/ANS00879.html>.

¹¹² Data source - IMS Health, National Disease and Therapeutic Index™, April 1994-March 2000, extracted 6/04.

¹¹³ FDA/CDER/ODS/DSRCS Review of average length of a prescription and average intended duration of therapy for ketorolac and bromfenac, dated July 13, 2004.

¹¹⁴ Public Health Advisory (1999) Trovan (trovafloxacin / alatrofloxacin mesylate) and risk of liver failure. FDA June 9, 1999. Available from: <http://www.fda.gov/cder/news/trovan/trovan-advisory.htm>.

failure appeared to be unpredictable, occurring after as few as two days exposure, but with a substantially increased risk noted in patients receiving the drug for longer than two weeks.¹¹⁵

Time-to event analysis (life-table estimation) showed an association between risk of developing ALF and duration of therapy with trovafloxacin. A background incidence rate for ALF due to idiopathic causes was estimated at one case per million per year. Based on the 14 reports of ALF received by the FDA over a two year period, the relative risk of ALF with trovafloxacin was shown to be above background from the start of therapy, and to increase rapidly with increasing duration of exposure.¹¹⁶

A Public Health Advisory was issued by the FDA in 1999 which effectively restricted use of this drug to hospitalized patients with certain serious life or limb-threatening infections. The efficacy of liver function monitoring in acceptably monitoring the risk of severe liver injury associated with trovafloxacin was considered uncertain. The manufacturer of trovafloxacin agreed to direct distribution of trovafloxacin only to pharmacies in inpatient health care facilities (i.e., hospitals and long-term nursing care facilities).¹¹⁷

F. Synopsis - RiskMAP tools for drugs that induce liver injury - track record of efficacy

Transaminase Monitoring

A rationale of regular serum transaminase monitoring is predicated on full characterization of the timing and tempo of liver injury as well as a high level of compliance by patients and physicians. In fact, the utility of transaminase monitoring in preventing severe DILI has never been convincingly demonstrated. Moreover, transaminase monitoring has been shown to be ineffective as a risk minimization tool in the case of troglitazone, isoniazid, and lovastatin (as described in previous sections of this review). Transaminase monitoring is ineffective when the tempo of liver injury is such that inexorable progression occurs even after the drug has been stopped in response to a signal of transaminase elevation. The foremost requirement that determines the usefulness of transaminase monitoring in preventing frank liver injury is that “the time interval between onset of liver chemistry abnormality and subsequent liver injury must exceed the screening interval.”¹¹⁸

This was not the case with troglitazone. An analysis of spontaneously reported cases of ALF associated with troglitazone showed that “progression to irreversible liver injury probably occurred within a one-month interval in most patients, casting doubt on the value of monthly monitoring” of serum transaminase levels as a means of preventing severe DILI.¹¹⁹ In addition,

¹¹⁵ *Ibid.*

¹¹⁶ Graham DJ, Ahmad SR, Piazza-Hepp T. (2002), *op cit.*

¹¹⁷ *Ibid.*

¹¹⁸ Adams PC, Arthur MJ, Boyer TD, DeLeve LD, et al. Screening in liver disease: Report of an AASLD Clinical Workshop. *Hepatology* 2004;39:1204-1212.

¹¹⁹ Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. *Am J Med* 2003;114:299-306.

despite a series of “Dear Healthcare Professional” letters recommending monthly monitoring, transaminase monitoring was not regularly performed.¹²⁰

With regard to the utility of transaminase monitoring as a method of minimizing risk of liver injury, Lee concluded in a recent review article¹²¹ that “monitoring is unlikely to be effective in the case of a rare adverse reaction. Monitoring is seldom performed consistently, and even if it were, it provides no guarantee of safeguarding the patient, since many drug reactions develop abruptly.” Rapid acceleration of liver injury in some individuals may preclude an absolute protective value of standardized periodic transaminase monitoring.¹²²

Limited Duration of Therapy

Hepatotoxicity was generally only observed with bromfenac in patients who took the drug for more than 30 days; however, despite attempts to regulate the duration of therapy by clear statements in product labeling, prescribers often did not heed this information and fatal liver injuries still occurred (as described previously in this review).¹²³

Although not primarily for reasons of hepatotoxicity, the USPI for Toradol (ketorolac tromethamine tablets) includes a boxed warning which states that the duration of use is “not to exceed 5 days because of the increased risk of serious adverse events.” An analysis (using data from IMS NPAPlus™)¹²⁴ of the average length of a prescription for oral ketorolac during the five year period from June 1999 to May 2004 showed a fairly consistent pattern, ranging from 5.1 to 7.3 days. Analysis of the average intended duration of therapy (using data from IMS NDTI™)¹²⁵ for oral ketorolac for patients seen by office-based physicians showed that, from May 2001 to April 2002, approximately 82% of prescribers intended patients to take ketorolac for a 5 day or less course of therapy. In 15% of mentions the intended duration of therapy was not specified.¹²⁶ It is not known whether, or to what extent, computer-based real-time notifications to retail pharmacists from pharmacy benefit managers (PBMs) regarding prescription days supplied in excess of recommendations (non-reimbursable claims) may influence appropriate duration of therapy for this product.

Restricted Access and/or Restricted Distribution

A Public Health Advisory was issued by the FDA in 1999 which effectively restricted use of trovafloxacin to hospitalized patients with certain serious life or limb-threatening infections. The efficacy of liver function monitoring in acceptably monitoring the risk of severe liver injury

¹²⁰ Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess M. Liver enzyme monitoring in patients treated with troglitazone. *JAMA* 2001;286:831-833.

¹²¹ Lee WM. 2003. *op cit*.

¹²² Avigan M. 2003. *op cit*.

¹²³ FDA Talk Paper. Wyeth-Ayerst Laboratories announces the withdrawal of Duract from the market. *op cit*.

¹²⁴ Data source - IMS Health, National Prescription Audit Plus™, June 1999- May 2004, extracted 6/04.

¹²⁵ Data source - IMS Health, National Disease and Therapeutic Index, May 2001-April 2004, extracted 6/04.

¹²⁶ FDA/CDER/ODS/DSRCS Review of average length of a prescription and average intended duration of therapy for ketorolac and bromfenac, dated July 13, 2004.

associated with trovafloxacin was considered uncertain. The manufacturer of trovafloxacin agreed to distribute trovafloxacin only to pharmacies in inpatient health care facilities (i.e., hospitals and long-term nursing care facilities).¹²⁷ These actions have resulted in a substantial decrease in trovafloxacin utilization, and a corresponding decrease in spontaneous reports of liver failure caused by this drug (there have been none reported to FDA since 1999).

Because of potential serious liver injury, as well as potential fetal damage if taken during pregnancy, Tracleer (bosentan), a drug recently approved for the treatment of pulmonary arterial hypertension in patients with Class III or IV heart failure, is only available through the Tracleer Access Program. FDA approval of this drug was contingent on several actions by the sponsor including 1) developing an enhanced prescriber educational program; 2) developing a program which ensures complete registration of all patients receiving Tracleer; 3) developing a program to provide complete registration and certification of practitioners who prescribe Tracleer; 4) developing a comprehensive program to track and report to CDER all severe liver injuries; and, 5) developing a monitoring program to facilitate on an annual basis an assessment of risk management goals.

The Tracleer™ Access Program (TAP) provides a toll free line to physicians with initial information about Tracleer, a site to report adverse events, and customer service. Following the toll-free call, a completed patient enrollment form is faxed to TAP to initiate the prescription, allowing a one month supply (with refills), providing patient information and including physician certifications. Each specialty distributor must agree to a defined set of rules to sell Tracleer, including insertion of patient reminders in the monthly prescription, generating a letter to the prescribing physician stating the prescription has been filled, calling the patient prior to shipment of the next month's medication supply and asking whether they've had a blood draw for liver tests, calling the physician if the patient has not had a test within the last month, and determining the reason if a planned refill does not occur. The patient enrollment form contains a statement: "I certify that I am prescribing Tracleer for this patient for a medically appropriate use in the treatment of pulmonary arterial hypertension, as described in the Tracleer full prescribing information. I have reviewed the liver and pregnancy warnings with the patient and commit to undertaking appropriate blood testing for monitoring liver function in this patient and testing for pregnancy (if the patient is a female of child-bearing potential)". This statement is followed by a place for the physician's signature.¹²⁸

Labeling

A recent study of FDA-approved product labeling for identified hepatotoxic drugs indicated that the Physicians Desk Reference for the year 2000 included black box warnings for severe liver toxicity for eleven non-generic drugs.

¹²⁷ *Ibid.*

¹²⁸ FDA/CDER. Regulatory Briefing for Tracleer (bosentan). dated October 23, 2001.

The labels for an additional 52 drugs were found to include Warnings or Precautions about liver failure and/or necrosis.¹²⁹ The utility of Warnings or Precautions in communicating risk information in an effort to prevent liver injury has not been systematically evaluated. However, several studies of particular drugs have found that product labeling may not meaningfully affect physician behavior.^{130 131 132}

¹²⁹ Willy ME, Li Z. What is prescription labeling communicating to doctors about hepatotoxic drugs? A study of FDA approved product labeling. *Pharmacoepi Drug Saf* 2004;13:201-206.

¹³⁰ Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride. *JAMA* 2000; 284:3036-9.

¹³¹ Walker AM, Bortnichak EA, Lanza L, Yood RA. The infrequency of liver function testing in patients using nonsteroidal anti-inflammatory drugs. *Arch Fam Med* 1995; 4:24-29.

¹³² Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess M. 2001. *op cit*.

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

Date: February 12, 2009

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Subject: Review of "Safety Surveillance Plan"

Drug Name(s): Rivaroxaban

Submission Number: Original NDA July 28, 2008

Application
Type/Number: NDA 022406

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 the proposed “safety surveillance plan” for rivaroxaban dated July 28, 2008 and submitted to OSE for consultation on December 17, 2008.

Rivaroxaban (BAY 59-7939) is a highly selective, direct factor Xa (FXa) inhibitor. The proposed indication is prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing total hip replacement (THR) or total knee replacement (TKR) surgery. The proposed dosing is 10 mg by mouth once daily for up to 35 days, and use does not require therapeutic blood monitoring. If approved as such, it may be appealing for broader use “off-label” in patients requiring long term anticoagulation. The sponsor is currently studying longer-term exposure indications, such as prevention of stroke and non-central nervous system systemic embolism in patients with nonvalvular atrial fibrillation.

2 MATERIAL REVIEWED

The following materials were reviewed:

- Sponsor’s proposed safety surveillance plan dated July 28, 2008
- Dr. Min Lu’s FDA mid-cycle clinical review slides dated December 2, 2008
- Proposed package insert dated July 28, 2008

3 RESULTS OF REVIEW

3.1 Overview of Clinical Program

There are two pivotal studies for each indication under current NDA review, THR and TKR. All four are randomized, double-blind, double-dummy, active-controlled studies. The active comparator for both indications was subcutaneous enoxaparin, which is approved and labeled for prophylaxis after both THR and TKR. The primary efficacy endpoint was a composite of all cause death, non-fatal PE, and proximal and/or distal DVT.

According to the sponsor’s submission, subjects were included who were scheduled for elective primary or revision THR or TKR procedures. Bilateral procedures were allowed if done during the same surgery. Exclusion criteria most relevant to this review were: 1) active bleeding or high risk of bleeding contraindicating treatment with low molecular weight heparin, and 2) acute clinical hepatitis, chronic active hepatitis, or cirrhosis. Liver panel testing was done on days 1, 6, 13, 36 or 42, and 65.

A total of 10,600 rivaroxaban subjects were evaluated for safety in 64 completed studies to date across all indications. Approximately 7,000 of these subjects were exposed to rivaroxaban for at least 12 days. The total patient denominators for adverse event analysis in the THR/TKR pivotal studies are rivaroxaban, 6183 and enoxaparin, 6200.

Regarding efficacy, the review division medical officer’s mid-cycle analysis pointed out that rivaroxaban showed statistically significant efficacy for the major endpoint, venous thrombosis, compared to the comparator in 3 of the 4 pivotal studies (all cause death shown as a safety endpoint):

No. events (%)	THR trial 1 (rivaroxaban vs enoxaparin)	THR trial 2 (rivaroxaban vs enoxaparin)	TKR trial 1 (rivaroxaban vs enoxaparin)	TKR trial 2 (rivaroxaban vs enoxaparin)
<i>Venous thrombosis</i>	1.1 vs. 3.7	2.0 vs. 9.3	9.6 vs. 18.9	6.9 vs. 10.1
Death all cause	0.3 vs. 0.3	0.2 vs. 0.7	0 vs. 0.2	0.2 vs. 0.3

3.2 Safety Concerns

3.2.1 Sponsor’s Safety Concerns

The sponsor identified two safety concerns:

- Identified risk: Bleeding events
Major bleeding was defined as bleeding that was fatal, into a critical organ, required re-operation, clinically overt extra-surgical site bleeding associated with a drop in hemoglobin ≥ 2 g/dL, or clinically overt extra-surgical site bleeding requiring transfusion of ≥ 2 units blood. These events occurred in less than 1% of subjects and the rates were similar for subjects in the rivaroxaban and enoxaparin arms.
- Potential risk: Transient elevation of liver laboratory tests
Of “transient elevation of liver laboratory tests”, the application states: “...cases of ALT levels $>3x$ ULN concurrent with total bilirubin levels $>2x$ ULN have been observed. The incidence of such cases is balanced on rivaroxaban and enoxaparin and most frequently occur after surgery within the first 2 weeks of study medication administration. The occurrence of such cases is most likely a consequence of surgery (i.e., reduced blood flow during surgery, hypoperfusion of liver) and associated medical procedures (i.e., blood transfusion and anesthesia)”.

3.2.2 FDA Safety Concerns

The review division medical officer’s mid-cycle review identified three major concerns:

- Bleeding events
- Cardiovascular events (ischemic stroke)
- Hepatic events

Hepatic events are the focus of this post-marketing risk management review. Bleeding is an expected consequence of products that decrease clotting, and is normally managed through recommendations and information in the professional package insert. Ischemic strokes,

recorded for 12 rivaroxaban patients vs. 7 in the comparator arm, are a clinical review issue related to both safety and efficacy, since the intended effect is anti-coagulation.

In the pivotal trials for THR/TKR, the overall death rate was higher in the comparator arm (0.21% vs. 0.40%). However, the FDA mid-cycle clinical review of the entire safety database showed that there were 3 deaths from liver failure in which rivaroxaban could not be excluded. Two of these cases occurred within the 30 day window of treatment duration proposed for the indications under review. In addition, there were six “possibly related” Hy’s law cases¹ among rivaroxaban patients in the THR/TKR trials compared to three in the enoxaparin² comparator arm.

3.3 Sponsor’s Safety Surveillance Plan

The sponsor submitted a “safety surveillance plan” including a pharmacovigilance plan whose stated objective is “...to systematically³ collect adverse events from multiple sources and to conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals”. As such, the pharmacovigilance plan is routine adverse event monitoring and reporting as per appropriate Regulations. In addition, the “safety surveillance plan” includes a risk mitigation strategy to minimize off-label use. Specifically, the objectives are:

- Rivaroxaban prescribed only for short term VTE prophylaxis in patients undergoing THR or TKR
- Rivaroxaban prescribed only for the recommended duration of therapy (14 days for TKR and 35 days for THR)
- Rivaroxaban not to be prescribed for unapproved indications

¹ FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation [DRAFT]. October 2007. *Hy’s law cases have the following components - 1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo. 2. Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN). 3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.*

² The labeling for enoxaparin includes the following information in the ‘Side Effects’ section: “Elevations of Serum Aminotransferases: Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Lovenox should be interpreted with caution.”

³ “systematically” is not defined

To meet these objectives, the sponsor proposes the following risk management elements:

- Professional labeling. The risk of hepatotoxicity is described primarily as elevations in liver function tests in the Adverse Reactions section. The sponsor proposes to contraindicate rivaroxaban use in patients with “hepatic disease associated with coagulopathy associated with clinically significant bleeding risk.” No liver monitoring plan was proposed in the labeling.
- “Targeted educational and outreach programs”. In summary, pertinent healthcare professionals (orthopedic surgeons, hematologists, hospitalists, and anesthesiologists, hospital and retail pharmacists, and nurses) will receive a launch information sheet/mass mailing. In addition, a product website, formulary kit, in-service programs, and toll-free medical information line will be developed. None of the materials were submitted. In absence of the materials, it is difficult to determine if they will serve an educational purpose or function primarily to advertise and promote rivaroxaban.

4 DISCUSSION

The sponsor has proposed a risk management program consisting of routine measures such as labeling, education (with targeted detailing by the sales force), and spontaneous adverse event reporting to assure appropriate prescribing consistent with the proposed indication. The routine nature of the sponsor’s proposal is explained by their conclusion to the pharmacovigilance submission: “...a Risk Minimization Action Plan is not needed for rivaroxaban because routine risk assessment and risk minimization measures, targeted educational activities and outreach programs can adequately address all the potential safety risks”.

A formal risk management plan⁴ that exceeds routine labeling and pharmacovigilance can be required if FDA finds additional measures are necessary to ensure that the benefits of the product outweigh the risks. In making this determination, the FDA Amendments Act (FDAAA) requires FDA to consider a number of factors including the estimated size of the population likely to use the drug, the seriousness of the disease or condition that is to be treated with the drug, the expected benefit of the drug, the expected or actual duration of treatment with the drug, and the seriousness of the known or potential adverse events that may be related to the drug.

Clearly, this assumes that the risks in question are manageable with available tools. Thus, REMS might not be appropriate in situations where the risk-benefit ratio is not acceptable for marketing with only routine risk management *and* the risks cannot be mitigated with a formal risk management plan. .

⁴ A formal risk management plan is called a “Risk Evaluation and Mitigation Strategy” or REMS. On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act (FDAAA) which amends the Federal Food, Drug and Cosmetic Act (FDCA) to authorize FDA to require a risk evaluation and mitigation strategy (REMS) when it is determined that additional measures are necessary to ensure the benefits of a drug outweigh the risks. (section 505-1(a)(1)).

If FDA's review is consistent with the sponsor's interpretation of rivaroxaban's safety database, we would not recommend any risk mitigation strategy other than routine measures. If, on the contrary, it is concluded that the observed liver injury cases are likely causally related to rivaroxaban use, or if the data relevant to a potential signal for severe drug-induced liver injury have not been fully characterized and assessed, then the sponsor's proposal would not be considered adequate to address the risk of drug induced liver injury (DILI).

The question then becomes whether the risk of DILI can be mitigated by a formal risk management plan. There are three main categories of risk management tools: Patient labeling (Medication Guides), Communication Plans, and Elements to Assure Safe Use (ETASU), which often involving some degree of restricted distribution.

- **A Medication Guide** for rivaroxaban could serve to alert patients to the warning signs of liver injury, thus increasing the timeliness of drug discontinuation and medical attention. However, it is unlikely that this strategy would prevent DILI, since some patients in the trials developed serious hepatic dysfunction despite robust clinical and laboratory monitoring.
- **Education/Communication Plans** are also unlikely to succeed at managing this severe potential toxicity. Education, in the absence of strategies to assure safe use, would encourage but not ensure safe use. Traditional risk communication tools such as labeling and Dear Healthcare Professional letters have been shown to have little impact on prescribing behavior or compliance with recommended laboratory monitoring^{5,6,7,8} For example, troglitazone was withdrawn from the market due to hepatotoxicity after several labeling changes and Dear Healthcare Professional Letters did not achieve meaningful or sustained improvement in liver enzyme testing.⁶
- **Elements to Assure Safe Use** may include any number of strategies such as mandatory prescriber, pharmacy, and/or patient enrollment in a program based on certification of education or special experience, required laboratory monitoring, and other measures to assure safe use. These strategies offer additional measures to mitigate harm, but are contingent on having an identifiable at-risk group and/or methodology to monitor for preventable harm. As noted above, some patients in the rivaroxaban trials developed serious hepatic dysfunction despite robust clinical and laboratory monitoring. Generally, the effectiveness of transaminase monitoring in preventing severe DILI in the post-marketing setting has not been convincingly demonstrated. This may reflect the fact that

⁵ Willy M, et al. *A study of compliance with FDA recommendations for pemoline (Cylert)*. J Am Acad Child Adolesc Psychiatry. 2002 Jul;41(7):785-90.

⁶ Graham D, et al. *Liver enzyme monitoring in patients treated with troglitazone*. JAMA. 2001 Aug 15;286(7):831-3.

⁷ Smalley W, Shatin D, Wysowski D, Gurwitz J, Andrade S, et al. *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*. JAMA 2000;284(23):3036-3039.

⁸ Weatherby LB, Nordstrom BL, Fife D, Walker AM. *The Impact Of Wording in "Dear Doctor" Letters and In Black Box Labels*. Clin Pharmacol Ther. 2002;72:735-742.

for some products, rapid acceleration of liver injury limits the protection afforded by periodic transaminase monitoring. Programs currently in place to manage hepatotoxic risk through periodic monitoring⁹ in the post-approval setting were implemented after considering a variety of factors. These include severity of the indicated disease and expected clinical benefit, availability of other treatment options, and severity of the hepatotoxic risk observed during drug development (for example, transient elevation of laboratory tests versus frank liver failure and/or death).

Limiting treatment duration through a risk management program could be a useful tool if there is a window of safe use that does not preclude efficacy. This might be an effective option for this product if suspect cases for rivaroxaban did not exist in the short-term use indications. Until/if a causal role for rivaroxaban in Hy's cases occurring within the 30-day exposure window is ruled out, limiting use to 30 days is not a useful risk mitigation strategy for this product.

5 RECOMMENDATIONS

If future safety data from on-going clinical trials indicate that rivaroxaban is likely causally associated with severe DILI, a formal risk management program with safe use strategies should be considered *if* the data identify the at-risk subpopulation and/or a monitoring approach that will prevent serious adverse hepatobiliary events. In the absence of such directive information, we believe additional risk management measures for rivaroxaban will not effectively minimize the risk of hepatotoxicity.

⁹ Tracleer (bosentan) Access Program (TAP) and Letairis (ambrisentan).Education and Access Program (LEAP); both programs address the risk of hepatotoxicity and teratogenicity, Promacta (eltrombopag) CARES program addresses the risk of hepatotoxicity along with a number of other risks. These 3 drugs carry Boxed Warnings with regard to the risk for hepatotoxicity.

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