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MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 4, 2004

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DRUG: Exanta™ Tablets (ximelagatran); NDA 21-686

SPONSOR: AstraZeneca

SUBJECT: Review of Risk Minimization Action Plan submitted December 23, 2003

PID: D040079

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REVIEW CONTENTS page

List of Abbreviations

ACS	Acute coronary syndrome
AF	Atrial fibrillation
ALT	Alanine aminotransferase
DCRDP	Division of CardioRenal Drug Products
DDRE	Division of Drug Risk Evaluation
DGCDP	Division of Gastrointestinal and Coagulation Drug Products
DILI	Drug-induced liver injury
DSRCS	Division of Surveillance, Research, and Communication Support
FDA	Food and Drug Administration
LTE	Long Term Exposure
MI	Myocardial infarction
NDA	New Drug Application
ODS	Office of Drug Safety
RiskMAP	Risk Minimization Action Plan
TBL	Total bilirubin
TKR	Total knee replacement
ULN	Upper limit of normal
VTE	Venous thromboembolism
VTE-P	VTE secondary prevention
VTE-T	VTE treatment

List of Definitions

?? **Severe Liver Injury**— defined as a concurrent increase in TBL >2 x ULN within 30 days of an increase in ALT >3 x ULN

?? **Fatal Liver Injury**—Death associated with severe liver injury or liver failure

?? **Surgical population**—data from 11 Phase II and Phase III studies of patients undergoing major orthopedic surgery (total knee replacement and total hip replacement) undergoing ximelagatran or comparator treatment for up to 35 days but mainly 7-12 days (n=15,740)

?? **Non-surgical population**—Data from 10 Phase II and Phase III studies (n=13,569) of patients with AF, VTE, or post ACS undergoing ximelagatran or comparator treatment for > 35 days up to 3 years and includes the Long term exposure (LTE) pool – 7 studies (N=13,147).

?? **Long-term Use**—refers to use $\geq$ 35 days

?? **Short-term Use**—refers to use < 35 days

?? **Short-term indication**—the short-term indication currently being sought is for the prevention of VTE in patients undergoing knee replacement surgery at 36mg bid for 7-12 days.

?? **Algorithm 1—**the trigger for weekly monitoring if ALT > 3 x ULN; for discontinuation if ALT > 7 x ULN (implementation of first amendment was approximated to 1 June 2000)

?? **Algorithm 2—**the trigger for weekly monitoring if ALT > 2 x ULN; for discontinuation if ALT > 5 x ULN (implementation of second amendment was approximated to 1 November 2001)

1 EXECUTIVE SUMMARY

The Office of Drug Safety (ODS) has reviewed the Exanta (ximelagatran) Risk Minimization Action Plan (RiskMAP) submitted by AstraZeneca as part of its new drug application (NDA 21-686) to address the risk of hepatotoxicity associated with long-term ximelagatran therapy. The RiskMAP does not address the possible risks of delayed hepatotoxicity after short-term use with ximelagatran, or the risk of myocardial infarction (MI) that was identified in the FDA Clinical Safety Review. In addition, reversal of excessive ximelagatran-induced bleeding was not addressed by the sponsor.

Ximelagatran is an anticoagulant and if approved, will be the first available oral direct thrombin inhibitor. The sponsor is seeking approval for three indications: 1) for the short term prevention of venous thrombo-embolism (VTE) in patients undergoing knee replacement surgery; 2) for the long-term prevention of stroke and other thromboembolic complications associated with atrial fibrillation; and 3) for the long term secondary prevention of VTE after standard treatment for an episode of acute VTE. In this document, we occasionally refer to the combined safety experience with long term exposure (LTE), which includes the treatment populations for indications (2) and (3).

LONG-TERM USE

During clinical development, at least 37 cases of severe liver injury [defined as alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN) with concurrent increase in total bilirubin (TBL) >2 x ULN] were observed among patients randomized to ximelagatran. The relative risk of severe liver injury was 6.6 (95% CI 2.6 – 16.9) compared to warfarin/placebo, with one affected person in 200 treated with ximelagatran. Preliminary analyses suggest the risk of severe liver injury begins within the first month of therapy.

Based on the observation of Hy Zimmerman[1] that at least 10% of individuals with severe drug-induced liver injury (as defined above) progress to liver failure, liver transplant, or death, ximelagatran-associated fatal liver injury or liver failure could occur in as many as 1 in 2,000 patients treated long-term (i.e., 10% of 1 in 200.) Consistent with this prediction, three deaths associated with severe liver injury occurred in the ximelagatran LTE clinical development program, for a proportion of one fatal liver injury in 2,300 patients exposed to ximelagatran (n=6948 ximelagatran treated patients, mean treatment duration of 357 days).

To address ximelagatran-induced hepatotoxicity associated with long-term use, the sponsor proposes an ALT-monitoring program similar to the program used during clinical development. This program consisted of baseline and monthly ALT assessments, with more frequent testing

[1] 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.

and discontinuation linked to different thresholds of ALT elevation relative to the upper limit of normal. The initial algorithm specified an ALT >7 times the ULN as a threshold for drug discontinuation, but this was revised to 5 times the ULN after the occurrence of a death associated with severe liver injury. Cases of severe liver injury and a case of fatal liver injury continued to be observed after the implementation of the revised algorithm. More conservative algorithms were not tested, so it remains unknown whether timely discontinuation with any ALT elevation can prevent irreversible life-threatening liver injury with ximelagatran.

The sponsor's proposed RiskMAP targets [ ] compliance with ALT monitoring and algorithm-triggered discontinuation. In the clinical development program, severe liver injury, including fatal liver injury occurred even though compliance with ALT testing and discontinuation met or exceeded 83%. The sponsor has not provided sufficient evidence about whether timely transaminase monitoring and early discontinuation of the drug at the first signs of liver toxicity could prevent severe liver injury and associated fatalities with ximelagatran. Even if evidence were sufficient to support the claim that monitoring can reduce the risk of severe liver injury and associated fatalities, the sponsor's projected lower adherence with recommended ALT monitoring in clinical use has the potential to result in a *higher* rate of severe liver injury and liver failure/fatal liver injury than was observed in clinical development.

The demonstrated severity and rate of hepatotoxicity is substantial with long term treatment with ximelagatran. Since no adequate mechanism to prevent or limit this toxicity has been demonstrated, there is no basis for proposing RiskMAP tools to reliably limit hepatotoxicity risk in individual patients.

Should it be determined that ximelagatran offers selected populations of patients sufficient benefits to counter the hepatotoxicity risk, consideration should be given to a restrictive RiskMAP that would limit risk on a population basis. One example might be a performance-linked access system with a registry for patients entering long-term ximelagatran therapy. Such a system should focus on appropriate education of patients and providers about risk, and appropriate patient selection. We would also advocate further quantification of the risk of hepatotoxicity over time, and clarification of the ability of ALT monitoring and early discontinuation of the drug to mitigate the risk of severe liver injury and liver failure/fatal liver injury.

SHORT-TERM USE

In comparison to warfarin controls, there does not appear to be an elevated risk of severe liver injury during the short-term use (<12 days) of ximelagatran. However, in the two pivotal studies of total knee replacement (TKR) patients, an imbalance in ALT > 3 x ULN was observed at the follow-up visit approximately 6 weeks after surgery in ximelagatran-treated patients (8 ximelagatran- vs. 1 warfarin-treated subject). Whether delayed onset of severe liver injury after short-term ximelagatran treatment could occur is unknown, since no additional routine study visits were conducted.

Analysis of data from the LTE population shows that initial signs of liver injury (ALT > 3 x ULN) were observed during the first month of ximelagatran therapy in 6 of 37 patients who went

on to develop severe liver injury (ALT > 3 x ULN and TBL > 2 x ULN). This suggests that severe liver injury can potentially begin during the first month of treatment with ximelagatran. Since practice guidelines recommend anticoagulation of certain high risk patients with TKR for more than 12 days, we anticipate physicians will want to treat some TKR patients for a longer period with ximelagatran. Since the risk of severe liver injury could increase with longer duration of ximelagatran therapy, even during the first month, "short-term" duration of use after TKR would need to be strictly limited to prevent potential severe liver injury.

The sponsor did not submit a RiskMAP to constrain ximelagatran use to a defined period (i.e., 7-12 days). Again, ODS remains concerned about the intrinsic risk and poorly characterized pace of hepatotoxicity with ximelagatran. Should the benefit of ximelagatran therapy be sufficient to warrant approval for short-term prevention of VTE in patients undergoing TKR, we recommend close discussion with FDA to design and implement a RiskMAP to assure that total duration of therapy in individual patients does not exceed 12 days or whatever interval is found to be appropriate.

We note other safety risks of ximelagatran may merit consideration of a RiskMAP. These include (1) the risk of MI identified in the FDA Clinical Safety Review**,** and (2) the absence of clear methods to control excessive bleeding with ximelagatran should it occur. Neither of these risks was addressed by the sponsor, and one or both may warrant exploration of various risk management tools.

2 INTRODUCTION/BACKGROUND

This consult follows a request by the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) to review a Risk Minimization Action Plan (RiskMAP) submitted for ximelagatran. The primary goal of the ximelagatran RiskMAP as stated by the sponsor is to optimize the benefit-risk of ximelagatran by minimizing the potential risk of severe liver injury in patients who present with an elevation in hepatic transaminases. This memorandum will include a review of the sponsor's RiskMAP in light of FDA experience with other drug products that also cause serious hepatic injury.

The RiskMAP does not address the risk for myocardial infarction (MI), as identified in the FDA Clinical Safety Review. ODS comments toward safety are restricted only to ximelagatran-induced hepatotoxicity. In addition, measures to be taken in the management of ximelagatran-induced bleeding have not been fully addressed by the sponsor.

2.1 PRODUCT INFORMATION

Ximelagatran is an anticoagulant and if approved, will be the first available oral direct thrombin inhibitor. It is a prodrug that is bioconverted to melagatran which is a potent, reversible, competitive and direct inhibitor of thrombin. Melagatran specifically inhibits thrombin versus other coagulation factors. Ximelagatran is approved in Europe for the short term prevention of VTE after knee surgery.

The sponsor is seeking approval for the following 3 indications:

?? For the prevention of VTE in patients undergoing knee replacement surgery at 36mg bid for 7-12 days.
?? For the prevention of stroke and other thromboembolic complications associated with atrial fibrillation at 36mg bid.
?? For the long-term secondary prevention of VTE after standard treatment for an episode of acute VTE at 24mg bid.

2.2 RISK ASSESSMENT

2.2.1 Risk Assessment with Short-term Use

The risk of liver injury with the short-term use of ximelagatran is largely uncharacterized. In the two pivotal Phase III studies of total knee replacement (TKR) patients (SH-TPO-0010 and SH-TPO-0012), there was no signal of an elevated risk of severe liver injury during the short-term use (<12 days) of ximelagatran in comparison to warfarin. It is not known whether delayed onset of clinically severe liver injury could occur after short-term (<12 days) ximelagatran therapy. Follow-up visits were conducted at 6 ± 2 weeks after TKR surgery. More ximelagatran-treated subjects were found to have ALT > 3 x ULN at the time of the follow-up visit, especially

at the higher dose [8 patients (0.5%) receiving ximelagatran vs. 1 patient (0.06%) in the warfarin group].[2] Routine study visits beyond 4 to 6 weeks post TKR were not conducted.

Analysis of data from the LTE population shows that severe liver injury can potentially begin during the first month of treatment with ximelagatran. Of 37 ximelagatran-treated patients identified as having severe liver injury (concomitant ALT >3x ULN and TBL >2x ULN), the initial onset of increased ALT was noted within the first 30 days of study treatment in six patients, and sponsor causality assessment was stated as "related" to ximelagatran for four of these six cases[3]. (The investigator considered the liver injury to be possibly related to study drug in one additional case which was disputed by the sponsor). In the comparator group (N=6230), only two such patients, who then went on to develop increased ALT and TBL, were found to have an increased ALT during the first 30 days of study treatment. Of these, one patient was considered by the sponsor to have drug-related liver injury.

Since the risk of severe liver injury with ximelagatran might begin as soon as the first month of therapy, "short-term" duration of use after TKR would need to be strictly defined in terms of minimal hepatotoxicity risk and limited accordingly.

2.2.2 Risk Assessment with Long-term Use

A significant risk for ximelagatran-associated liver injury has been identified in the long-term exposure (LTE) population. There were 37 (0.5%; n=6948) ximelagatran-treated patients[4] in the LTE population who developed severe liver injury defined as a concurrent increase in TBL >2 x ULN within 30 days of an increase in ALT >3 x ULN, compared to 5 (0.08%; n=6230) in comparator groups, relative risk=6.6 (95% confidence interval 2.6 – 16.9).

In addition to an imbalance in cases of severe liver injury in ximelagatran-treated patients, two other observations also support a causal association of liver injury with ximelagatran. First, in the LTE population, an increase in ALT > 3 X ULN was observed in 6 to 13% of ximelagatran-treated patients, compared to 0 to 2% in comparator groups. Second, an assessment of likelihood of causality by the sponsor also shows increased risk of severe liver injury with ximelagatran.[5] Based on clinical and diagnostic information obtained at the time of liver injury, such assessments of causality of individual cases may complement the measurement of relative rates among the treatment groups of the randomized clinical studies. In 19/6948 ximelagatran-treated patients who developed severe liver injury, the sponsor indicated that liver toxicity was causally related to study drug. In contrast, in only 2/6230 patients assigned to comparator, severe liver injury was considered related to study drug. *Based on the sponsor's causality assessment the relative risk of severe liver injury ximelagatran in study treatment related cases is high and statistically significant; relative risk 8.52 (95% CI 1.98 - 36.56).*

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[2] Sponsor's Tables 2.7.4SP.7.5-17 and 5-18.

[3] Sponsor's Table 2-8 in Part 1 Response – Non-surgical population, in Safety data request (May 13, 2004). Patient ID #s: SH-TPA-0003-105-1967 (day 7, related), SH-TPA-0005-200-8434 (day 22, related), SH-TPC-0001-259-0007(day 28, related), SH-TPC-0001-338-1440 (day 16, related), SH-TPV-0002-265-5442 (day 9, unrelated – sponsor assessment, possibly related – investigator assessment), SH-TPC-0001-348-2065 (day 27, unrelated).

[4] Sponsor identified 36 patients in LTE group that experienced concomitant TBL > 2 x ULN and ALT > 3 x ULN, one additional case (SH-TPA-0005-3030-7859) identified in the DGCDP medical officer review.

[5] Sponsor's Table 2-8 in Part 1 Response – Non-surgical population, in Safety data request (May 13, 2004).

Additional analyses of drug-related liver injury cases (based on sponsor's causality assessment) which also include cases that did not meet the cut-off for severe liver injury as defined in this consult (i.e., concurrent ALT > 3 X ULN and TBL > 2 X ULN), also showed a highly significant relative risk for ximelagatran-treated patients vs. comparator. As indicated in Sponsor's Table 2-8, there were a total of 66 ximelagatran-treated patients in the LTE pool who developed concurrent increases in TBL > 1.5 X ULN and ALT > 3 X ULN. Of these, 45 cases (0.65%) were considered related to ximelagatran treatment.[6] In contrast, as noted in Sponsor's Table 2-14, there were a total of 11 cases which met this lab value cut-off in the comparator group,[7] of which only 5 cases (0.08%) were considered drug-related by the sponsor (relative risk 8.1, 95% CI 3.2 – 20.3).

In two additional cases of severe liver injury (SH-TPA-0003-309-2522 and SH-TPV-0002-265-5442), the investigator considered the liver injury to be possibly related to ximelagatran therapy, although the sponsor considered it to be unrelated. Also, one additional case of fatal liver injury (SH-TPA-0005-3030-7859) which was considered by the investigator to be possibly related to study drug was not included in the sponsor's analysis.

Alternative explanations for severe liver injury in ximelagatran cases judged by the sponsor to be unrelated to study drug included active cancer, hepatic congestion associated with heart failure, cholelithiasis, concomitant therapy with flucloxacillin, sepsis, hepatitis B, and mechanical biliary obstruction. Alternative explanations for comparator cases included active cancer. Taken together with the previously mentioned findings, the striking imbalance in the number of unrelated cases in the ximelagatran treatment group vs. comparator suggests that ximelagatran therapy may have caused or contributed to severe liver injury in some of the unrelated cases, as well.

It is notable that there were three deaths associated with ximelagatran associated hepatocellular necrosis leading to liver failure or reduced clotting factors synthesis. These are briefly summarized below.

- SH-TPA-0005-0620-7259: 80-year-old male developed increased ALT after 56 days of ximelagatran 36 mg bid; drug stopped on day 88; ALT 1502 U/L, TBL 2.4 mg/dL on day 100; liver biopsy showed acute submassive necrosis on day 108; death due to GI bleed from duodenal ulcer on day 143; investigator considered liver failure related to ximelagatran.
- SH-TPA-0005-3030-7859: 77-year-old male developed increased ALT after 57 days of ximelagatran 36 mg bid; drug stopped on day 74; hospital admission with GI bleed (ALT 569 U/L, TBL 6.2 mg/dL) on day 75; respiratory failure and death due to coagulopathy on day 76; investigator considered events possibly related to ximelagatran.[8]

[6] Sponsor's Table 2-8 in Part 1 Response – Non-surgical population, in Safety data request (May 13, 2004).
[7] Sponsor's Table 2-14 in Part 1 Response – Non-surgical population, *op cit*.
[8] This patient was identified by the DCGDP medical reviewer as meeting criteria for severe liver injury (TBL > 2 x ULN and ALT > 3 x ULN)

?? SH-TPV-0002-265-5442: 73-year-old male with fulminant hepatitis B died from hepatic failure after 24 days of ximelagatran 36 mg bid; investigator considered events possibly related to ximelagatran.

The sponsor's analysis of potential risk factors predisposing to liver injury (ALT > 3 x ULN) in the ximelagatran treatment group versus comparator showed increased risk in the post acute coronary syndrome population, patients treated for venous thromboembolism, female patients, patients with low body mass index, and patients receiving concomitant therapy with statins. However, the sponsor concluded these relationships were *not* strong enough to recommend that any patients with these attributes should not be given ximelagatran.[9]

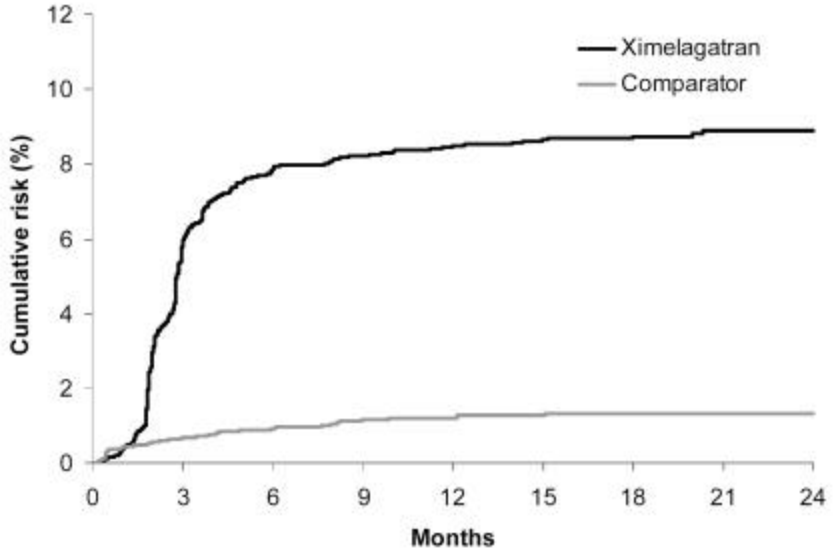
2.2.3 Risk Assessment Over Time

Thus far, the sponsor's evaluation of the risk of hepatic injury with ximelagatran has been primarily focused on the occurrence of isolated elevation of serum ALT (>3xULN). The sponsor's analysis of cumulative risk of hepatic injury is presented in Figure NP31 (reproduced below). However, ODS believes that cases of severe liver injury (defined as concurrent elevation of ALT and TBL) are of greater prognostic significance in evaluating the potential impact of ximelagatran-associated hepatotoxicity. This belief is based on a guiding principle, articulated by Hy Zimmerman and referred to as "Hy's Law", that seeks to correlate clinical trial experience with projected risk of severe liver injury.[10] ODS has requested additional analyses from the sponsor which will look at cumulative risk of concurrent ALT and TBL elevations observed during the ximelagatran clinical program (pending at the time of writing).

[9] He, R. Clinical Review of NDA 21-686 Ximelagatran; Indications: Prevention of VTE in patients undergoing knee replacement surgery; Secondary prevention of VTE after standard treatment for an episode of acute VTE. (draft executive summary).

[10] 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.)

Figure NP 31 **Cumulative risk of ALAT >3xULN (%) versus time after randomization (ITT population): LTE pool – Central laboratory data only**



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 in his textbook,[11] and has since been proven true for drugs including bromfenac, dilevalol, troglitazone, and trovafloxacin.[12]

Zimmerman noted that drug-induced hepatocellular jaundice is a serious lesion, with mortality ranging from 10 to 50 percent.[13] 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 having death as an outcome [14]. 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.[15]

2.2.4 Projection of Severe Liver Injury and Liver Failure in the Postmarketing Setting

As noted above, the clinical development program for ximelagatran shows that long-term use of ximelagatran can cause severe liver injury and liver failure/fatal liver injury in some patients. Furthermore, cases of severe and fatal liver injury occurred under the ALT monitoring algorithm proposed within the RiskMAP, the more stringent of two algorithms used in the clinical development program. In the clinical development program, compliance rates were higher than

[11] 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.
[12] CDER Drug-induced liver toxicity. 2000. *op cit.*
[13] 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.
[14] CDER. Drug-induced liver toxicity. 2000. *op cit.*
[15] *ibid.*

those projected by the sponsor for the postmarketing setting. Thus, we project that the frequency of severe liver injury observed in the general population will be equal to or greater than that observed in the clinical trials. As noted previously in this review, the frequency of severe liver injury observed in the LTE population was 0.53% for ximelagatran-treated patients versus 0.08% for patients randomized to warfarin or placebo; relative risk=6.6 (95% confidence interval 2.6 – 16.9). Based on a hypothetical scenario of 100,000 patients in the general population exposed to ximelagatran for a similar treatment duration, and managed by health care providers as seen in the long-term clinical trials, we could then expect some 500 individuals to develop severe ximelagatran-associated liver injury, including 50 patients (10%) who would progress to fulminant liver failure, liver transplant, or death.

2.3 COMPLIANCE WITH THE ALT TESTING IN THE XIMELAGATRAN CLINICAL TRIALS

The sponsor's review of compliance in the clinical trials was evaluated in terms of adherence to serum ALT testing as described in the study protocols and compliance with discontinuing ximelagatran. Data regarding compliance with recommended testing is limited to patients who were identified to undergo weekly testing, and did not examine compliance with routine testing (monthly) among all patients. Compliance with ALT testing was determined by comparing the date of when the test occurred versus when it should have occurred. This review of compliance with hepatic monitoring during the clinical trial revealed the following:

Compliance with Weekly Monitoring

Patients were considered compliant with weekly monitoring if the serum ALT was performed within 1 to 10 days of previous test. For patients monitored under algorithm 1, about 70% of patients identified to undergo weekly serum testing (those with ALT >3 x ULN), were monitored within 10 days of the increased ALT. For patients monitored under algorithm 2, the compliance decreased to about 63%. Nonetheless at least 30% of patients that were identified to undergo weekly monitoring under either algorithm were considered non-compliant.

Percent reaching Discontinuation Level

Of patients who met the threshold for ximelagatran discontinuation[16], those initially identified with elevated ALT levels[17] before they reached the level of discontinuation increased from 39% to 49%, following the implementation of algorithm 2. Nevertheless, under either algorithm, at least 50% of the patients who were discontinued did so without a preceding ALT value above the algorithm threshold for triggering weekly monitoring.

For those that were not identified before they reached the ALT levels of discontinuation, it is not clear if the reason was noncompliance with monitoring or that the rate of ALT increase was too rapid for timely detection of rising levels by the monitoring scheme outlined in either of the two algorithms.

[16] An elevation of ALT > 7 x ULN for algorithm 1 and ALT >5 x ULN for algorithm 2
[17] An elevation of ALT > 3 x ULN for algorithm 1 or ALT > 2x ULN for algorithm 2

Impact of Monitoring on Discontinuation

Approximately 83% of patients monitored according to algorithm 1 who developed an ALT > 7 x ULN discontinued ximelagatran. This rate of discontinuation increased to 93% in the patients who developed an ALT > 5 x ULN when monitored under algorithm 2 which requires weekly monitoring of those patients with ALT > 2 x ULN.

It is unclear why 7 and 17% of ximelagatran treated patients who met the threshold ALT levels for discontinuation under algorithms 2 and 1, respectively, failed to do so and what impact this had on patient outcomes.

Compliance in Patients with Severe Liver Injury

DDRE examined the impact of monitoring on discontinuation among the subset of 36 patients who were identified by the sponsor with concurrent elevations in serum ALT >3x ULN and TBL >2x ULN (defined in this review as severe liver injury). In this group of patients, 23 of these 36 patients were monitored under algorithm 1, and 13 under algorithm 2. Fourteen (39%) of these 36 patients failed to discontinue study drug at the correct time, and of these, nine patients did not recover to TBL =1x ULN and ALT =2x ULN.[18]

We note that among the three cases of fatal liver injury; two patients were monitored under algorithm 1 and one was monitored under algorithm 2.

- SH-TPA-0005-0620-7259 was monitored under algorithm 1. At month 2, his serum ALT was mildly elevated but less than the 3 x ULN threshold that required weekly monitoring. The following month his ALT >20 x ULN. He discontinued ximelagatran; however, he progressed to fatal liver injury.

  Compliance with algorithm 1 in this case did not prevent liver failure. Based upon this case, the sponsor modified the algorithm so that the threshold for weekly monitoring was lowered to an ALT of > 2 x ULN.

- SH-TPV-0002-265-5442 was monitored under algorithm 2. Nine days after starting ximelagatran, his serum ALT was mildly elevated (60 U/L). He was diagnosed with Hepatitis B and was hospitalized on day 18. On day 24 ximelagatran was discontinued. Two days later his ALT > 10 x ULN and TBL was 4 mg/dL. He progressed to liver failure and died.

  This patient developed rapid liver injury that may not have been preventable by any transaminase monitoring.

- SH-TPA-0005-3030-7859 was presumably monitored under algorithm 1 based on therapy and event dates. At month two, his serum ALT was elevated to 4.5 x ULN (216 U/L) a value which did not meet the threshold of discontinuation, using algorithm 1. He was scheduled to undergo weekly testing but he was non-compliant with weekly testing.

[18] Sponsor's Table 4-6 in Part 1 Response – Non-surgical population, in Safety data request (May 13, 2004).

Two weeks later, he was admitted with severe coagulopathy, ALT 569 U/L, TBL 6.2 mg/dL, and a fatal upper gastrointestinal bleed.

This patient was identified as requiring weekly testing but was not compliant. Use of algorithm 2 would not have changed the outcome in this case because the patient did not reach ALT values at the time of his month two visit which would have signaled discontinuation utilizing either algorithm.

Median Compliance to Algorithm 2

For the ximelagatran SPORTIF V trial, in which clinicians were educated and reinforced on the importance of applying the LFT-testing algorithm, median compliance with the algorithm was 83%.[19]

3 PROPOSED RISK MINIMIZATION ACTION PLAN

3.1 GOALS AND OBJECTIVES

The primary goal of the ximelagatran RiskMAP as stated by the sponsor is to optimize the benefit-risk of ximelagatran by minimizing the potential risk of severe hepatic injury in patients who present with an elevation in hepatic transaminases.

The RiskMAP objectives are to:

- ?? Facilitate compliance of the monitoring recommendations by healthcare workers and patients
- ?? Minimize the risk of severe hepatic injury

3.2 TOOLS

The sponsor has proposed recommending voluntary ALT monitoring via professional labeling and associated educational support initiatives to address the risks associated with the long-term or chronic use of ximelagatran. The sponsor has not proposed reminder system tools, which are systems that help reinforce desired behaviors by involving additional processes or paperwork to usual prescribing or the use of performance linked access system (PLAS) or restricted distribution systems which link drug product access to compliance with RiskMAP elements.[20]

3.2.1 Proposed Labeled Recommendations to Monitor ALT

The ALT monitoring recommended in the labeling would consist of the following:

1. Obtaining baseline ALT; if < 2 x ULN, patient may initiate ximelagatran
2. Screen ALT monthly

[19] Ximelagatran Risk Minimization Action Plan (NDA 21-686 Amendment June 2004); Edition No. 1: pg 40.
[20] Please refer to the draft guidance, Development and Use of Risk Minimization Action Plans, March 2004 at http://www.fda.gov/cder/guidance/5766dft.htm for further details.

a. If < 2 x ULN, continue to screen monthly for 6 months and periodically thereafter
b. If > 2 x ULN, monitor ALT weekly; stop drug if:
    i. ALT > 3 x ULN after 4 weeks
    ii. ALT > 5 x ULN at anytime
    iii. Symptoms of hepatic injury (e.g. jaundice w/o obvious cause)

This algorithm is the more stringent of two algorithms utilized during the clinical trials.

3.2.2 Targeted Education and Outreach Communication

The sponsor has submitted a comprehensive educational plan to address the risk of severe liver injury associated with the long-term use of ximelagatran by promoting compliance with ALT monitoring. As stated in the October 2003 ODS review[21], a wide array of educational tools are planned for physicians, pharmacists and patients to achieve the steps outlined in the Medication Administration and Use Process.[22] Qualitative and quantitative field testing have been conducted with physicians, pharmacists, and patients. Pharmacists' and physicians' reactions to each tool were evaluated for the tool being easy to understand and useful as well as having the ability to help manage the ALT testing requirements. Patient comprehension and acceptance of materials were examined.

Positive aspects include an analysis of the medication administration and use process, development of redundant interventions based on analysis, use of adult learning principles, involvement of stakeholders in the process and field testing of tools and materials. An additional positive aspect is that the RiskMAP is planned to be integrated at launch into the marketing messages for Exanta®.

However, education as the sole mechanism to modify physician behavior with regard to appropriate laboratory monitoring is concerning. The sponsor acknowledges, and we agree, that labeling and other modalities to communicate laboratory monitoring recommendations have been largely unsuccessful. [23, 24] Additionally, the educational tools are quite extensive and we have concerns about the ability of stakeholders to incorporate the elements (curriculum, algorithm, worksheets, flowsheets, patient reminders, etc.) into daily practice. The educational program also does not focus on messages that would limit the duration of use of the ximelagatran should only the short-term indication be approved. Moreover, there is no evidence that education alone will successfully drive the Medication Administration and Use Process and lead to compliance with monitoring recommendations.

3.3 EVALUATION PLAN

The evaluation component of the RiskMAP is designed to assess:

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[21] See Memorandum from DDRE and DSRCS to Robert L. Justice, MD, October 6, 2003 for Feedback on ximelagatran (Exanta™) risk management briefing document dated July 31, 2003**.**

[22] Ximelagatran Risk Minimization Action Plan (NDA 21-686) Document No. CV.000-114-526, Edition No. 1; Figure 3, pg 17.

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

[24] Graham et al. Liver enzyme monitoring in patients treated with troglitazone. JAMA. 2001 Aug 15;286(7):831-3.

?? Actual compliance by healthcare providers and patients with ALT testing recommendations
?? Occurrence of hepatic outcomes measured through both pharmacovigilance and pharmacoepidemiologic methods.

3.3.1 Proposed Compliance with ALT Testing

The sponsor proposes monitoring ALT algorithm compliance following the launch of ximelagatran through various databases and offers the following metrics to determine RiskMAP success or if additional actions are indicated. These metrics are based upon three sources of data which the sponsor considers to be "benchmarks" for "an appropriate ALT-testing compliance target for ximelagatran".[25]

?? The sponsor proposes a target mean compliance level of [ ] for with ALT-testing postmarketing. They assert that this level of compliance roughly corresponds to the levels observed with warfarin INR monitoring in a similar patient population.
?? If ALT monitoring falls between [ ], then relevant aspects (not defined by sponsor) of the RiskMAP will be evaluated.
?? They consider a compliance level of less than [ ] to be unacceptable and if ALT testing falls below this value, then additional action(s) or substantive changes in the program will be implemented. Details concerning the additional actions or changes were not provided.

3.3.2 Measuring Hepatic Outcomes

The sponsor has proposed monitoring for serious hepatotoxic adverse events through spontaneous post-marketing surveillance, special agreements with registries of acute liver failure (e.g., the Acute Liver Failure Group), and by analyzing the [ ] database 12 months post launch and every six months thereafter to assess rates of events in the population of interest.

To our knowledge the sponsor has not assessed the power of [ ] to detect an effect within 12-18 months given the projected level of use within the [ ] population. The sponsor has not offered targets for rates of serious hepatotoxicity or liver failure that are acceptable/ unacceptable and would trigger additional actions or modification of the RiskMAP.

3.3.3 Comments on Proposed Evaluation Plan for Risk Management

Specific comments on the metrics of the proposed evaluation plan and the methods proposed to measure compliance and hepatic outcomes will be deferred until the Advisory Committee has commented on the potential benefits of ximelagatran in short-term and long-term treatment, and the appropriateness of the tools proposed as well the possible need for additional tools to address the risk of hepatotoxicity.

4 RECOMMENDATIONS FOR ADDITIONAL RISKMAP OPTIONS

[25] Ximelagatran Risk Minimization Action Plan (NDA 21-686 Amendment June 2004) pgs 35-48.

The development and/or strategies around a RiskMAP for ximelagatran depend largely upon the risk assessment and the benefit-risk profile of ximelagatran for each of the proposed indications. Two of the proposed indications (prevention of stroke in patients with AF and secondary prevention of VTE) are for the long term use (> 35 days) of ximelagatran and the third indication (prevention of VTE following knee replacement surgery) involves short term therapy of 7-12 days of ximelagatran.

The risk management considerations outlined below take into account the different risk profiles that are related to the proposed short-term and long-tem indications. Two risk management scenarios will be considered. These include:

?? Use of Ximelagatran for short-term indications only
?? Use of Ximelagatran for both short-term and long-term therapy.

4.1 CONSIDERATIONS IN RISK MANAGEMENT OF XIMELAGATRAN IF APPROVED FOR SHORT-TERM USE ONLY

There does not appear to be a high risk of severe liver injury during the short-term use (<12 days) of ximelagatran relative to warfarin. However, the risk of severe liver injury for the short-term use has not been fully characterized. The time at which the risk of severe liver injury begins to rise is largely unknown but appears to be within the first month of therapy.[26] This finding suggests the importance of limiting the duration of ximelagatran therapy to 12 days of therapy to avoid risk of severe drug-induced liver injury (although it does not provide assurance that a delayed-onset of injury after cessation of exposure cannot occur with this drug).

A brief overview of published medical literature regarding state-of-the-art treatment in managing thromboembolic risk in knee replacement surgery has revealed that recommendations for extended prophylaxis beyond the 12 post-surgical days are supported by clinical data.[27] A meta-analysis of studies evaluating outcomes in 13,169 total hip replacement (THR) and total knee replacement (TKR) patients who received 7 to 10 days of anticoagulant prophylaxis after surgery determined that a significant risk for thromboembolism was present.[28] The authors concluded that, without extended prophylaxis beyond 10 days, nonfatal venous thromboembolism will occur in approximately 1 of 32 patients and fatal pulmonary embolism will occur in approximately 1 of 1000 patients within three months of surgery. Risk stratification, including a checklist which can be used to aid surgeons in deciding which patients have post-operative risk factors that warrant extended prophylaxis after hospital discharge, has been recommended by some authors.[29] *If the risk of long-term use of ximelagatran is determined to outweigh the benefit, and practice guidelines encourage extended therapy for some patients in the post-surgical setting (e.g. TKR), voluntary compliance with limited duration of therapy may be difficult to achieve.*

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[26] See Section 2.2.1 Risk Assessment with Short Term Use, pg 7-8 of this document.
[27] Colwell CW. Managing thromboembolic risk in hip and knee arthroplasty: state of the art. *Orthopedics* 2003;26(2):s231-236.
[28] Douketis JD, Eikelboom JW, Quinlan DJ, Willan AR, Crowther MA. Short duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of prospective studies investigating symptomatic outcomes. *Arch Int Med* 2002;162:1465-71.
[29] Friedman RJ. Extended thromboprophylaxis after hip or knee replacement. *Orthopedics* 2003;26(2):s225-230.

Experience with other drugs suggests that attempting to limit the duration of therapy to minimize the risk of hepatotoxicity via labeling has had mixed results. Bromfenac was a drug labeled for short-term use but marketed to a patient population with a high percentage of individuals suffering from chronic pain and seeking long-term analgesic treatment.[30] Analysis of drug utilization[31] during the two years prior to bromfenac's withdrawal from the market (1997-1998), shows that approximately 10-20% of bromfenac mentions in outpatient office visits 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.[32] More recent experience with ketorolac has been more encouraging. Ketorolac is a nonsteroidal anti-inflammatory drug, indicated for use up to 5 days in adults.[33] An analysis of the average length of a prescription[34] 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. 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 ketorolac or any other drug products, such as ximelagatran.

If the benefit of ximelagatran for the prevention of VTE in patients undergoing TKR outweighs the risk, and it is approved for the short-term use of 7-12 days, we recommend the goal of the risk management be to strictly limit the duration of use to 12 days or less, thereby minimizing the risk of hepatotoxicity associated with longer use. We offer the following risk management options for consideration for the short-term use of ximelagatran but acknowledge that there is a paucity of data on the effectiveness of these methods to limit duration of therapy.

a) Labeling

?? boxed warning to limit therapy to <12 days to avoid risk of severe drug-induced liver disease, including acute liver failure

b) Education

?? of prescribers and patients (and possibly PBMs) about need to limit duration of therapy to avoid severe drug-induced liver disease, including acute liver failure

?? should contain the appropriate safety messages for indication

?? should reach the appropriate target audience of prescribers, pharmacists, and associated allied health professionals

?? if patient comprehension studies are to be conducted that the Sponsor assess comprehension with open-ended questions rather than alternate-response items since the open-ended format allows respondents to demonstrate comprehension through translation and interpretration of information

[30] See Appendix 1-Drug induced liver injury, pgs 33-34.
[31] Data source - IMS Health, National Disease and Therapeutic Index™ , April 1994-March 2000, extracted 6/04.
[32] 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.
[33] Physician Desk Reference-Toradol® Professional Label, Roche Laboratories September 2002.
[34] Data source – IMS Health, National Prescription Audit *Plus*™ (NPA *Plus*™), June 1999-May 2004, extracted 6/04.

- ?? Sponsor should submit draft or mock print copies of educational materials to DDMAC for their review prior to launch
- ?? Patient Starter kit should be available not only in physician offices but other areas of distribution such as pharmacies, managed health care organizations, and hospitals
- ?? All prescribing physicians, those that are visited by a sales representative and those that are not visited, should receive the same materials.
- ?? Since the results of field testing[35] indicated that physicians want programs that are "simple, practical, patient-oriented, and do not increase cost and/or workload" and pharmacists want programs that "do not disrupt the normal work flow" the Sponsor should consider evaluating the actual use of the program to determine the ability of stakeholders to incorporate the elements (curriculum, algorithm, worksheets, flowsheets, patient reminders, etc.) into daily practice.

c) Special conditions of dispensing

- ?? special packaging – such as a dosepak with no more than a 12-day supply
- ?? dispensing limited to inpatient pharmacy following post-operative procedure – feasibility of this approach requires discussion with clinical and payor community

d) Provision of a physician /patient agreement (for charting)

- ?? Patient signs to indicate awareness of risks and that therapy should be limited to no more than 12 days.
- ?? MD signs to attest that product use is warranted and appropriate and the prescription will be limited to duration of 12 days.

e) Voluntary limitation of advertising/promotion options- examples include:

- ?? Limited professional promotion to specific, defined specialties and journals
- ?? No DTC advertising to reduce pressure to prescribe this particular product.
- ?? FDA approval of launch and all marketing materials for a limited and well-defined period of time
- ?? Very limited or no product sampling
- ?? If sampling is done, consider attestation by the physician to provide no greater than a 12 day supply to patients.

f) Performance-linked Access System (PLAS)

- ?? Limit distribution to inpatient hospital pharmacies that would agree to dispense:
    - o No greater than a 12-day supply with no refills or new prescriptions for a patient that has received the product in a specified period of time.
    - o Dispense to only patients that have an ALT of < 2 x ULN
    - o No distribution of product to retail pharmacies

The utility and feasibility of serum ALT testing for short-term use does not appear relevant for two reasons: 1) a signal of hepatotoxicity has not been demonstrated in the clinical trials for the short-term use of ximelagatran although full risk assessment was incomplete and 2) monthly monitoring has been recommended by the sponsor, and therefore patients would not be treated with ximelagatran long enough for monitoring to occur. Baseline serum ALT testing, as was done as a basis for exclusion from study, could be considered. However it is unknown whether patients with an elevated ALT at baseline are at increased risk of serious hepatotoxicity relative to patients with normal baseline ALT values.

[35] Ximelagatran Risk Minimization Action Plan (NDA 21-686 Amendment June 2004) pg 12.

Whatever tools are selected for appropriate risk management for this product for short-term therapy, it is essential that the sponsor develop a comprehensive evaluation plan to determine the effectiveness of the program, accompanied by timely plans of action if stated goals are not met.

4.2 CONSIDERATIONS IN RISK MANAGEMENT OF XIMELAGATRAN IF APPROVED FOR LONG-TERM USE

Utilization of ximelagatran for long-term therapy is complicated by the appearance of a strong signal for serious, ximelagatran-associated hepatotoxicity observed in the long-term clinical trials. The sponsor has submitted a RiskMAP based on monthly ALT screening ["ALT algorithm"]. As outlined by the sponsor, the stated goal for this RiskMAP would be to maximize compliance with the ALT algorithm, including assessment of baseline LFT status, monthly monitoring, and application of the weekly testing and possible drug discontinuation based on ALT elevations. *This scenario assumes that progression of liver injury can be mitigated through monitoring liver function tests at a proven interval. ODS notes the absence of data to support this assumption.*

The sponsor proposes a commitment to monitor compliance with the ALT algorithm for patients on therapy with ximelagatran through observational databases. However, experience with a number of agents including troglitazone, pemoline, and isoniazid suggest that such programs utilizing transaminase monitoring have been generally ineffective.[36, 37]

In the case of troglitazone, 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.[38] 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 (within a one month interval) of liver injury to a state of irreversibility. 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 ALF led to a boxed warning 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,[39] the use of pemoline dropped off substantially over the next five years,[40] and no additional drug-related cases of liver failure were subsequently

[36] See Appendix 1-Drug induced liver injury, pgs 35-7.
[37] Lee WM. Drug-induced hepatotoxicity. N Engl J Med 2003; 349:474-85.
[38] Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess M. Liver enzyme monitoring in patients treated with troglitazone. *JAMA* 2001;286:831-33.
[39] 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.
[40] FDA/CDER/ODS/DSRCS Review of the Proposed Risk Management Communication Plan for Cylert (pemoline) dated January 16, 2004.

reported to FDA.[41] Extensive clinical experience with isoniazid, a drug which can cause a more chronic liver injury pattern, has shown that risk of severe hepatotoxic reactions can be effectively minimized by instructing patients to stop drug and immediately report symptoms of liver injury as soon as they occur.[42] 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.[43, 44] Conclusions based on recent studies were that due to the course of liver injury in most isoniazid users who develop hepatocellular necrosis, clinical evaluation as the primary monitoring method is often effective. Moreover, the 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.[45]

Notwithstanding serious reservations that have been described and in light of the projected risk of severe liver injury, the following risk management tools might be considered if the product is approved for the long-term use.

a) Labeling

?? strengthen the label to a boxed warning, and strengthen patient education materials, a medication guide which clearly describes the risk associated with treatment.

b) Education

?? should reach the appropriate target audience of prescribers, pharmacists, and associated allied health professionals such as nurse practitioners, physician assistants, and anticoagulation clinic managers identified in field testing

?? if patient comprehension studies are to be conducted that the Sponsor assess comprehension with open-ended questions rather than alternate-response items since the open-ended format allows responsdents to demonstrate comprehension through translation and interpretration of information

?? Sponsor should submit draft or mock print copies of tools to DDMAC for their review prior to launch

?? Patient Starter kit should be available not only in physician offices but other areas of distribution such as pharmacies, managed health care organizations, and hospitals

?? All prescribing physicians, those that are visited by a sales representative and those that are not visited, should receive the same materials.

?? Since the results of field testing (see pg.12 of RMP) indicated that physicians want programs that are "simple, practical, patient-oriented, and do not increase cost and/or workload" and pharmacists want programs that "do not disrupt the normal work flow" the Sponsor should consider evaluating the actual use of the program to determine the ability of stakeholders to incorporate the elements (curriculum, algorithm, worksheets, flowsheets, patient reminders, etc.) into daily practice.

c) Provision of a physician /patient agreement (for charting)

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

[42] 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

[43] *ibid*.

[44] Lee WM. 2003. *op cit*.

[45] 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.

- ?? The patient signs to indicate awareness of risks and that safe use includes baseline and monthly liver function monitoring.
- ?? MD signs to attest that product use is warranted and appropriate and that he/she will conduct the required laboratory monitoring.

d) Voluntary limitation of advertising/promotion options

- ?? Limited professional promotion to specific, defined specialties and journals
- ?? No DTC advertising to reduce pressure to prescribe this particular product.
- ?? FDA approval of launch and all marketing materials for a limited and well-defined period of time
- ?? No product sampling

e) Performance-linked Access System (PLAS)

- ?? Mandatory registration of all patients
    - ?? Requirement for all patients to have baseline and monthly monitoring
- ?? Limit distribution to pharmacies that would agree to dispense:
    - ?? To only patients that present with ALT <2x ULN
    - ?? No refills
    - ?? Dispense no more than a 30 day supply

If ximelagatran long-term therapy is found to offer a substantial and important benefit that offsets the risk of severe drug-induced liver injury, and is approved on this basis, we recommend that consideration be given to the use of a PLAS. The goals for PLAS could be several fold: 1) To improve compliance with ALT-monitoring, although we acknowledge that in the case of ximelagatran treatment, serum ALT monitoring has not been proven to prevent progression to liver failure; 2) To identify and limit product use to subpopulations of patients for whom the benefits exceed the risks; and 3) to accurately quantify the frequency or incidence and range of severity of most/all ximelagatran-associated hepatotoxicity cases post-marketing. Data from this cohort could then quantify if the frequency of serious, ximelagatran-associated hepatotoxicity approximates 0.5% (1 in 200) as seen in the clinical trials, or, based on application of the 95% CI, closer to 1 in 460 (2.6x control) or 1 in 70 (16.9x control). By prospective recruitment and collection of data, this cohort would also further define qualitative data, such as potential risk factors for serious, ximelagatran-associated hepatotoxicity.

Whatever tools are selected for appropriate risk management for this product for short-term and long-term therapy, it is essential that the sponsor develop a comprehensive evaluation plan to determine the effectiveness of the program, accompanied by timely plans of action if stated goals are not met.

5 DISCUSSION

The sponsor has submitted a RiskMAP based on voluntary monthly ALT screening ["ALT algorithm"] via product labeling. As outlined by the sponsor, the stated objectives for this RiskMAP are to facilitate compliance of the monitoring recommendations by healthcare workers and patients through education and to minimize the risk of severe liver injury. The ALT-testing is designed to address the risk of hepatotoxicity associated with long-term treatment (>35 days) with ximelagatran.

Success in minimizing the risk of severe liver injury associated with long-term use of ximelagatran with serum ALT monitoring is contingent on two assumptions: 1) monitoring ALT with discontinuation of ximelagatran at pre-specified levels of ALT elevation would be effective in reversing the severe liver injury and so preventing serious sequelae and death and 2) patients and healthcare workers will be compliant with monitoring. There are no data to support the first assumption. In fact, at least one and possibly three cases of liver failure occurred in the ximelagatran clinical trials despite protocol requirements for transaminase monitoring and patient follow-up. Regarding the second assumption, the sponsor acknowledges that compliance with ALT-testing observed in the clinical trials as well as postmarketing laboratory monitoring of other hepatotoxins and warfarin show imperfect compliance and as such have set a target rate of compliance of ALT monitoring for ximelagatran post-marketing at [ ]. This target is less than what was achieved in the clinical trials. Based on the rates of severe liver injury observed in the long-term clinical trials, if the drug is approved and this program implemented, we anticipate at least 500/100,000 individuals treated with ximelagatran for long-term indications might develop severe ximelagatran-associated liver injury, including 50 (10%) with severe manifestations who could progress to liver failure, liver transplant, or death.[46]

The sponsor has not submitted risk management material directed towards restriction of ximelagatran to a defined period (i.e., 7-12 days) relevant for a short-term indication, nor suggested further assessment other than observational studies after marketing to examine the frequency or risk factors for ximelagatran-associated severe liver injury. It is of concern that some patients after TKR may require anticoagulation for substantially long than 12 days. In addition, prior experience with certain products labeled for short-term use only and associated with hepatotoxicity after a longer period of use (e.g., bromfenac) has demonstrated the difficulty in preventing risk for serious outcomes. Additional risk management measures, based in part on a thorough assessment of the benefit-risk profile that characterizes ximelagatran for each of the proposed short-term and long-term indications, should be discussed pending approval for marketing.

6 CONCLUSION/RECOMMENDATIONS

SHORT-TERM USE ONLY

If the benefit of ximelagatran therapy is determined to warrant approval for short-term prophylaxis for prevention of VTE in patients undergoing TKR, we recommend implementation of a risk minimization action plan designed to assure that total duration of therapy in individual patients will not exceed 12 days. This should include at a minimum labeling (boxed warning), education, special packaging and conditions of dispensing, a physician/patient agreement, limits on promotion, and consideration of restricted distribution. If approved with a RiskMAP, it is also essential that the sponsor develop a comprehensive evaluation plan to determine the effectiveness of the program, accompanied by plans of action if stated goals are not met.

LONG-TERM USE

[46] CDER Drug-induced liver toxicity. 2000. *op cit*.

If the benefit of long-term ximelagatran therapy is determined to exceed its risk of hepatotoxicity, we recommend restricted distribution measures to limit population risk. For example, approval could be conditioned upon establishment of a performance linked access system including a mandatory patient registry for patients entering long-term ximelagatran therapy. Other risk management tools, such as restricted distribution, labeling (boxed warning), physician /patient agreement, limitation in promotion, and education would require additional consideration. If a RiskMAP is employed, it is also essential that the sponsor develop a comprehensive evaluation plan to determine the effectiveness of the program, accompanied by plans of action if stated goals are not met.

As noted above, we do not agree that the sponsor's proposed RiskMAP for minimization of ximelagatran-associated severe liver injury is adequate. To date, serum transaminase monitoring in ximelagatran treated patients has not been demonstrated to be effective in preventing idiosyncratic severe drug-induced liver injury. Currently, the proposed monitoring plan provides no guarantee of safeguarding the patient from developing a rapid onset and life-threatening reaction.

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]

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[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]

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[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 troglitazone[72] 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.

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[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 die[80]. 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

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[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 trials[82], 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 Program[85] 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

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[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_Rezulin.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_Rezulin.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 Graham[90] 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*

Months 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

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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]

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[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,

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[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 article[121] 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 NPA*Plus*™)[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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