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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-427

Medical Review #2

9/13/03

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 21427
SPONSOR: Lilly
DRUG: Duloxetine
MATERIAL SUBMITTED: Response to Approvable Letter
DATE SUBMITTED: March 24, 2003
REVIEWER: Roberta L. Glass, M.D.
REVIEW COMPLETION DATE: September 10, 2003

I. BACKGROUND

The original NDA application for this submission was submitted on 11/12/01 for the use of duloxetine in the treatment of major depressive disorder in adults. FDA sent the sponsor an approvable letter on 9/13/02, which included requests for more information regarding syncopal events, abnormal liver chemistries, worldwide regulatory status, a safety update, and a commitment to long term study. The current submission was considered to be a complete response to the approvable letter and included the sponsor's proposed labeling based on FDA recommendations. The sponsor has also included two new full study reports (HMAYa and HMAYb) in an effort to support the use of higher dosing and provide more safety information. In this review, the dosing issue will be discussed in addition to an efficacy review of Study HMAYa; Study HMAYb was a failed/negative study, and will not be reviewed in great detail in this review. This review will address each topic discussed in the approvable letter of September 13, 2002, and also comment on the sponsor's proposed labeling.

Of note, \square

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II. ISSUES RAISED IN THE APPROVABLE LETTER OF 9/13/02

A. CLINICAL/STATISTICAL/CLINICAL SAFETY (SAFETY UPDATE)

1. SYNCOPE CASES

In response to the approvable letter, the sponsor provided additional information regarding the following six patients who had a syncopal episode during treatment with duloxetine.

- a. Patient 010-1919, a 64 yo Caucasian male, reported a syncopal episode after 48 days of duloxetine 40 mg bid. The patient reported having loss of consciousness after drinking champagne, but no blood alcohol level was obtained. The only significant history is that the patient reported "achiness" and headache for the three days prior to the episode which was attributed to the study medication, as there were no other concomitant medications at the time of the event. Cardiac problems were ruled out by the an internist; blood pressures ranged from 120-158/68-90 with no report of hypotension, laboratory or ECG abnormalities. The patient was able to complete the trial for 25 more days without any event reported.
- b. Patient 132-4201, a 49 y.o. Caucasian female, reported "overwhelming weakness" after two days of duloxetine 60 mg qd, and discontinued duloxetine after five days of treatment because of this

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event of weakness. Two days after discontinuing the medication, the patient reported that her weakness affected her ability to eat and drink. The sponsor explains that because of her inability to care for herself adequately, she became dehydrated and experienced a syncopal episode one day after discontinuing the study.

- c. Patient 111-2109, a 58 year old Caucasian female was reported to have dizziness with no loss of consciousness; therefore, this case appears to have been miscoded for syncope.
- d. Patient 101-111, a 25 y.o. Caucasian male reported "fainting" 39 days after starting duloxetine (dose is unclear). The patient reported dizziness and fatigue starting the day prior to the event which did not resolve until one day after duloxetine was discontinued (approximately 13 days after the syncopal event). Post baseline ECGs were not obtained. The patient's blood pressure during the trial ranged from 130-150/80-106 without reported differences between supine and standing blood pressures.
- e. Patient 024-3316, a 57 y.o. Caucasian female experienced a syncopal event after 8 days of duloxetine treatment. This patient also experienced amnesia, somnolence, abnormal thinking, diarrhea, impaired coordination and tremor during the trial and had dose adjustments to lower dosing prior to the event (from duloxetine 40 mg bid to 20 mg bid). The patient discontinued due to the syncopal event. At baseline, supine blood pressure was 138/90 mmHg with heart rate 76; one day prior to the syncopal event, blood pressure was 159/90 mmHg with heart rate of 68 bpm. No ECGs were reported.
- f. Patient 117-2753, a 67 y.o. Caucasian male, experienced a syncopal event 48 days after taking duloxetine 60 mg qd. The patient reported having a black out for an unknown period of time; upon returning to consciousness, he found dried blood from a scratch on his forehead and pain in his right shoulder and forehead. The patient had a history of a myocardial infarct in 1974 with catheterization and bypass surgery in 1975; baseline ECGs were normal. Upon referral to a cardiologist for this syncopal event, it was determined that there was no cardiac cause. The patient discontinued the study drug after this syncopal event.

Comment: Although it is difficult to determine the exact cause of the 5 cases of syncope described above (one case was miscoded and should have been dizziness), it is likely that duloxetine contributed to the occurrence of these episodes. Therefore, it would be helpful to have syncope listed as an adverse event in the labeling.

2. ABNORMAL LIVER EVENTS

Please refer to FDA reviews by John R. Senior, M.D (ODS: HFD-400: 7/31/03 & 8/27/03) and Zili Li, MD, MPH (HFD-580: 8/25/03) for a full discussion of the updated liver information submitted by the sponsor.

As described in the medical officer review of HFD-580 (Zili Li, MD, MPH: 8/25/03), duloxetine is associated with an increase in liver enzymes. In clinical trials, abnormal ALT tests were observed at a greater percent of patients in duloxetine treated groups compared to placebo groups (10.6% vs 7.7%). There were three female subjects identified with an abnormal liver enzyme > 10 times the upper limit of normal without jaundice (Subjects 120-3009, 105-1523, and 114-6708). There were also three male subjects identified (Subjects 500-5254, A09505, and A07606) who had abnormal ALT with hyperbilirubinemia (Subject 500-5254 had jaundice and ascites); it is also noted that these three men had a history of alcohol use prior to the reported liver injury. There were no liver transplantations or deaths observed attributed to liver failure. Dr. Li did not feel that there was conclusive evidence suggesting that duloxetine alone causes severe liver injury; however, this potential is not excluded. Empirical evidence suggests that alcohol use/abuse may increase the risk of liver injury, and Dr. Li recommends contraindicating duloxetine use in patients who are or may be likely to abuse alcohol.

In the Office of Drug Safety consult (ODS: HFD-400: 7/31/03), Dr. Senior recommends that duloxetine not be administered to patients who are or may be abusing alcohol, and suggested advising patients taking duloxetine to either abstain from alcohol use or to only drink lightly. He also recommends that patients with pre-existing liver disease be monitored (biweekly X4 and monthly x4) for ALT, AST, ALP,GGT, and TBL. Dr. Senior's recommendations also include a large safety study to detect the incidence of liver injury induced by duloxetine in addition to toxicology studies assessing the combined effects of duloxetine and excess alcohol.

Further review is being conducted on one new case of elevated liver function tests (Patient F1J-MC-HMBT-305-3512), a 60 year old female who developed elevated liver enzymes and hyperbilirubemia after 19 weeks of duloxetine therapy (please see sponsor submission of 8/15/03) with recovering liver function tests after drug termination. Dr. Senior did an initial consult on this case (ODS: HFD-400: 8/27/03) and concludes that the case was a "mild duloxetine-related hepatotoxic event," that may have been triggered by a second drug (i.e. acetaminophen?, alcohol?), and recommends follow up information. Additionally, there is a recommendation to have the Armed Forces Institute of Pathology review the liver pathology studies of Subject 500-5254.

3. WORLD WIDE REGULATORY STATUS

At this time, duloxetine is not marketed anywhere in the world. The following table submitted by the sponsor summarizes the status of duloxetine in various countries for both indications of major depressive disorder :

Indication	Country of Submission	Date of Submission	Application Status	<i>Estimated Decision Time</i>
MDD	UNITED STATES	12 Nov 2001	Approvable	25 Sep 2003

4. WORLDWIDE LITERATURE SEARCH

The sponsor submitted 28 abstracts and articles (mostly abstracts) as their response to FDA request for an updated report on the world's archival literature pertaining to the safety of duloxetine. These abstracts and articles did not provide any new safety data.

This reviewer was unable to locate a statement from the sponsor regarding who and how the search was conducted and that the literature was systematically, and in detail, reviewed and the findings.

5. SAFETY UPDATE

The cut-off date for this submission was November 1, 2002. Since the last safety update (11/01/01), there have been 2 studies completed and 4 ongoing studies for the indication of major depressive disorder. For all indications, the sponsor reports that completed studies include 2 clinical pharmacology studies, and 7 clinical studies (2 in major depressive disorder, 2 in patients with pain, and 3 in patients with stress urinary incontinence). There are currently a total of 17 ongoing clinical studies for all indications (4 in depression; 3 in patients with pain, 10 in patients with lower urinary tract disorders).

For the indication of major depressive disorder (MDD), the adverse events listed as reasons for discontinuation were comparable for the updated placebo-controlled database and the original NDA database. The sponsor identified the following four new adverse events that were reported as reasons for discontinuation that occurred in this most recent update: abdominal distension, psychotic disorder NOS, depression aggravated, and exacerbation of major depressive disorder, NOS.

Deaths reported in this safety update for MDD are presented in the following table. At this point in time, there does not appear to be a causal relationship between the event of death and the use of duloxetine.

Table 1: Deaths reported in the safety update for Major Depressive Disorder

PATIENT #	GENDER	AGE	TREATMENT GROUP	CAUSE OF DEATH
148-5809	F	44	Duloxetine 40 mg bid	Pulmonary edema; on drug for six months prior to event.
143-5313	F	23	Duloxetine 60 mg bid	Completed suicide
154-6409	F	53	Placebo	Completed suicide

The following is the sponsor's table listing deaths and other serious adverse events in ongoing duloxetine clinical studies for the indication of MDD.

Table 2: Listing of deaths and other serious adverse events in ongoing MDD duloxetine trials

Patient Number	Study	Indication Under		Adverse Event Term
		Investigation	Treatment Group	
304-3429	HMBC	MDD	Duloxetine 60 mg QD	Suicide attempt
401-4116	HMBC	MDD	Duloxetine 60 mg QD	Anxiety, Depression
501-5104	HMBC	MDD	Duloxetine 60 mg QD	Atrial fibrillation
600-6010	HMBC	MDD	Duloxetine 60 mg QD	Feeling ill
601-6106	HMBC	MDD	Duloxetine 60 mg QD	Lightheadedness, Confusion
601-6109	HMBC	MDD	Duloxetine 60 mg QD	Right arm lacerations
601-6127	HMBC	MDD	Duloxetine 60 mg QD	Suicide
606-6630	HMBC	MDD	Duloxetine 60 mg QD	Suicide attempt
608-6804	HMBC	MDD	Duloxetine 60 mg QD	Unstable angina
608-6806	HMBC	MDD	Duloxetine 60 mg QD	Suicide ideation
703-7301	HMBC	MDD	Duloxetine 60 mg QD	Chest pain
102-1102	HMBY	MDD	BLINDED	Syncope
105-1412	HMBY	MDD	BLINDED	Suicide attempt
008-4231	HMCB	MDD	BLINDED	Nephrolithiasis

For the indication of major depressive disorder, the common treatment-emergent adverse events reported in this update were comparable to the original NDA safety data base. There were no unexpected events reported.

It is difficult to comment on the events observed for the indications other than MDD.

Many of the patients had events which may have been exacerbated by their primary illness, as well as having the increased risk factor of older age. With the exception of liver compromise, events occurring in indications other than MDD will not be discussed in this review. Please refer to Sponsor Table 5.8 in the current safety update for a listing of deaths and other serious adverse events in ongoing duloxetine clinical studies for indications other than MDD.

6. POSTMARKETING (PHASE 4) COMMITMENT

In response to the approvable letter, the sponsor stated their view that they have fulfilled their commitment to studying duloxetine for long term effects. They have proposed that the following studies will have fulfilled this commitment and are proposing that they do not need to do any further studies:

a. The two studies of HMA Y (a and b) in patients with MDD (study reports are included in this submission) provide data from two studies utilizing an 8 week double-blind, placebo and comparator (paroxetine) controlled design of patients diagnosed with major depressive disorder; the 6 month continuation phase enrolled approximately 759 patients. From the study reports, it appeared that there was a completion rate of > 50% in both studies, with the exception of the placebo arm in study HMA Y a.

b. The ongoing study HMBC is a double-blind, placebo-controlled, parallel group relapse prevention study including approximately 245 patients diagnosed with major depressive disorder. HMBC is designed with a 12 week open label phase in which approximately 490 patients receive 60 mg duloxetine qd, followed by a 26 week double-blind continuation phase in which responders in phase 1 are randomized to placebo or duloxetine 60 mg qd. The study concluded with a 1 week follow up phase for safety. Rescue procedures during the continuation phase allow for placebo patient to receive duloxetine 60 mg qd, and patients receiving duloxetine 60 mg qd to receive duloxetine 60 mg bid.

c. HMA U, a completed open-label study, dosed patients on 120 mg/day in patients with MDD for up to one year (submitted in the original NDA submission).

Comment: From a safety perspective, the sponsor appears to have provided data for up to 1 year in open label and parallel group studies. Although some patients are exposed to anti-depressant medications for greater than a year, it is likely that many treatments are completed within a year.

From an efficacy perspective, the sponsor has not yet demonstrated efficacy beyond an acute treatment phase. Therefore, it is recommended that the sponsor conduct a relapse prevention study to determine long term efficacy. Although it would be optimal to have a one year relapse prevention study, it is possible that the sponsor's design of the ongoing study HMBC, a six month relapse prevention study, would fulfill the Phase 4 commitment to address the longer-term effectiveness of duloxetine for the treatment of major depressive disorder.

III. DOSING ISSUES

The sponsor has proposed that the starting dose for duloxetine be 60 mg/day rather than 40 mg/day providing the argument that there was a greater effect size observed at 60 mg/day. The sponsor also is

proposing that the dose range be expanded to 40 to 60 mg/day based on the data from the two study reports (HMAYa and HMAYb) included in this recent submission.

In summary, Study HMAYa, a placebo and comparator controlled 9 week study conducted in non-US countries, provided data supporting the efficacy of the doses of duloxetine 40 mg bid and 60 mg bid when using an LOCF analysis. Study HMAYb, with an identical design to HMAYa, was a failed study when viewing the LOCF analysis (the primary statistical analysis approach) and is not reviewed in depth in this review.

For more details of the design and analysis of both studies HMAYa and HMAYb, please refer to Appendices A and B of this review, and also to the FDA statistical review by Ohidul Siddiqui, Ph.D.

Unfortunately, there isn't a single study in which the 20 mg bid, 40 mg bid, and 60 mg bid could be compared head-to-head. Therefore, in his statistical review, Dr. Siddiqui calculated the effect size of the studies supporting the efficacy of duloxetine and summarized these findings in his review with the following table.

Table 3 Effect Size: Duloxetine vs. Placebo
(This table is extracted from the statistical review by Dr. Siddiqui)

	U.S. STUDIES			NON U.S. STUDY	
	HMAT		HMBH	HMAY	
	Duloxetine 40mg/day (20mg bid)	Duloxetine 80mg/day (40 mg bid) ¹	Duloxetine 60 mg QD ²	Duloxetine 80 mg/day (40 mg bid) ³	Duloxetine 120 mg/day (60 mg BID) ³
Change in HAMD17 Total score	.29	.35	.38	.76	.68

¹ Duloxetine 40 mg/day and 80 mg/day came from pooled data from Studies HMATa and HMATb;

² Duloxetine 60 mg/day came from pooled data from Studies HMBHa and HMBHb.

³ Duloxetine 80 mg/day and 120 mg/day came from pooled data from Studies HMAYa and HMAYb;

Non-U.S. countries: BG=Bulgaria, HR=Croatia, RO=Romania, RU=Russia, HU=Hungary, PL=Poland, SK= Slovakia .

Referring to Table 3 (above), Dr. Siddiqui comments that there is some discrepancy in the effect sizes when comparing the U.S. and Non U.S. studies with the range for the U.S. studies being .29 to .38 whereas the range for the Non-US studies is much higher at .68 to .76. Dr. Siddiqui suggests that this finding may be due to other factors (e.g. cultural, medical facilities, etc), and then questions if it is valid to compare the U.S. and Non-US studies. He also notes that the effect size appears to decrease for the higher dose of 120 mg/day compared to 80 mg/day (.68 vs .76) further complicating the use of effect size from the Non U.S. studies as supporting data for a higher initial dose.

As can be seen from Table 3 (above), the effect size for 60 mg qd is greater than the effect size for 80 mg qd (.38 vs. .35 respectively). The effect size of the dose 40 mg qd (.29) is comparable to the higher dosing. Given this information, Dr. Siddiqui concludes his review by recommending that the initial starting dose of 40 to 60 mg qd is appropriate for the duloxetine labeling.

There continues to be a lack of evidence providing a clear advantage of dosing 40 mg daily vs 80 mg daily; however, the sponsor has shown in Study HMAyA that duloxetine at doses of 40 mg bid and 60 mg bid demonstrate a statistically significant improvement in depression when compared to placebo.

Comment: Based on previously submitted data, the dose of 20 mg bid was shown to be statistically significant when compared to placebo (Study HMAyB). It would appear to be logical to recommend the lowest effective dose as the initial dosing. It is common clinical practice to titrate to a higher dose, if needed. It would seem to be in the best interest of the patient to begin with the lowest effective dose to decrease the dose dependent adverse event (e.g. dizziness, dry mouth, and blood pressure elevation) which, in and of themselves could affect compliance, especially in the beginning of treatment. The labeling could also reflect that efficacy has been demonstrated at dose up to 60 mg bid of duloxetine. The sponsor has not yet adequately addressed whether there is a clear advantage to the higher doses, and would probably need to conduct a head to head comparison study powered to detect that difference.

IV. LABELING ISSUES

The following labeling recommendations are based on the sponsor's proposed annotated labeling.

Under **Special Populations Section:**

- p. 3 **Renal Insufficiency:** Because of the increases in Cmax and AUC of the parent drug and metabolites observed in patients with end stage renal disease and severe renal insufficiency, it would be advisable to not administer this drug to patients suffering with this extent of renal compromise.
- p.3 **Hepatic Insufficiency:** Given that duloxetine appears to have caused hepatic injury in some individuals who did not previously have evidence of hepatic injury (i.e. elevated liver enzymes, jaundice, or ascites), it is questionable if this drug should be administered to any individuals who have a pre-existing liver condition. At a minimum, as recommended by Dr. Senior (Consult: 7/31/03), special observation and periodic monitoring (biweekly x4 and monthly x4 of serum ALT, AST, ALP, GGT, and TBL) will be needed for patients with pre-existing liver disease (chronic hepatitis B or C, alcoholic or non-alcoholic fatty liver disease with or without steatohepatitis, primary biliary cirrhosis or sclerosing cholangitis, α 1-antitrypsin deficiency, hemochromatosis, Wilson's disease or other problems).

Under **Indications and Usage Section:**

- p.7 The sponsor has proposed modifying the last paragraph of this section \mathcal{L}
It is recommended that the original FDA proposed language be restored, as the effectiveness of duloxetine in long-term use for major depressive disorder for longer than 9 weeks has not been systematically evaluated.

Under **Contraindications Section:**

Narrow-Angle Glaucoma: The sponsor has proposed to qualify the contraindication to **Uncontrolled** Narrow Angle Glaucoma. It is recommended that this be acceptable providing that an additional statement be added to **Precautions** (as was done in the labeling for Effexor, another SNRI) that "mydriasis has been reported in association with duloxetine; therefore patients with raised intraocular pressure or at risk of acute narrow angle glaucoma should be monitored."

Under WARNINGS Section:

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Under PRECAUTIONS Section:

General

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Comment:

Duloxetine demonstrated a dose dependent increase in the mean supine systolic and diastolic blood pressure seen in placebo controlled studies (please refer to Appendix C for a table of mean blood pressure changes extracted from Dr. Andreason's primary review of duloxetine) indicating that this drug does have the potential to cause hypertension. Given that there is a dose dependent increase in blood pressure, and that the sponsor is proposing to recommend the higher dosing of up to duloxetine 60 mg bid, it would be important to monitor blood pressure. Also, because duloxetine (like the marketed SNRI venlafaxine) may be used chronically, it would be prudent to monitor blood pressure and follow up any elevated readings.

It is recommended that the labeling language reinstate the FDA proposal with a precaution to monitor blood pressure periodically. It is also recommended that the inclusion of percentage tables in the labeling under **Adverse Reactions: Vital Sign Changes** Section be reinstated to help physicians judge the individual risk for their patients.

p. 9 **Use in patients with Concomitant Illness:** The sponsor increased the number of electrocardiograms to 321, which adds an additional 178 from the studies HMAyA and b. The design for the HMAy studies only had a post-baseline ECG obtained at termination without a specified time (i.e. it is possible that patients no longer had any drug in their blood stream). It would appear that the number of ECGs should be — the number of originally submitted ECGs.

Also, taking into account that the review division for HFD-580 had concerns that the sponsor has not adequately worked up duloxetine for QTc prolongation, it may be premature to make a statement that "the data indicate that duloxetine is not associated with the development of clinically significant ECG abnormalities.

ADVERSE REACTIONS Section

p. 13: It is unclear how the sponsor calculated the patient-years exposure. It is possible that they included exposure of duloxetine in indications besides major depressive disorder. If the sponsor has included patients from trials other than the indication of MDD, then it is recommended that this be described in labeling.

p. 14 **Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials**

The sponsor has omitted the table displaying the incidents of the events of nausea, dizziness and somnolence, and have omitted dizziness and somnolence as common adverse events identified as reasons for discontinuation. It is recommended that these events be described either in text or a table. Ideally, a table lends itself to a quicker reference for physicians.

It should also be made clear if the population being discussed includes patients with indications other than MDD.

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p. 15 For the Table of Treatment-Emergent Adverse Events Incidence, the sponsor has omitted the section which refers only to MDD patients. It is recommended that this be reinstated, as patients with MDD may have unique adverse events compared to other indications that this drug may be used for. It is also recommended that the table clearly describe other indications that make up the total "N."

p. 16 **Adverse Events section on Male and Female Sexual Function**

It appears that the sponsor has attempted to use the same language for this section that has been introduced into the labeling for SSRIs. Most of this language is reasonable, but it is questionable if reference to the SSRI effects is necessary. It is also recommended that the sponsor's "Table 2" be modified so that it is clear that the numbers are a percentage and not a number of incidents (i.e. put a "%" sign next to the numbers in the labeling).

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DOSAGE AND ADMINISTRATION Section

Please refer to discussion above (Section III). As recommended by FDA statistician Dr.Siddiqui, there is enough evidence to support an initial starting dose as 40 to 60 mg a day.

V. RECOMMENDATIONS/CONCLUSIONS

Please see the above discussion under Section IV (above) for labeling recommendations.

The data presented is sufficient to support efficacy claims for the use of duloxetine for the indication of major depressive disorder. Up to this point, the sponsor has not demonstrated that duloxetine ⌊

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Of concern are the case reports of liver injury associated with exposure to duloxetine. Up to this point three of the four individuals reported to have evidence of liver injury also reported a history of alcohol use. In the fourth case, it is unclear if there was concomitant use of another drug, but there is a strong signal that this hepatotoxic event was related to the use of duloxetine. If approved, at a minimum, it is recommended that there be a strong warning against the concomitant use of alcohol and duloxetine. This poses a difficult clinical dilemma, as many patients suffering from depression also drink alcohol recreationally, habitually, or in an effort to momentarily alleviate symptoms. Routine liver function tests should be considered. If marketed, duloxetine will have to be monitored closely for its potential to cause liver toxicity.

It is also noted that, upon review of duloxetine for [redacted], there was a major concern identified regarding insufficient information to conclude that duloxetine has no significant prolongation effect on the QT interval at doses in the proposed labeling [redacted]. It was requested that the sponsor conduct a study assessing the effects of duloxetine on the QTc interval following maximal potential interaction between duloxetine and the combination of CYP1A2 and 2D6 inhibitors. It would also be helpful to rule out QTc prolongation in the target population for patients suffering with major depressive disorder; therefore, it is recommended that the protocol for this study expand the population to include men and women of child bearing potential.

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APPENDIX A

Study HMAYa

Investigators/Location

This study was conducted at 21 investigators at 21 sites located outside the USA (Bulgaria, Croatia, Hungary, Poland, Romania, Russia, and Slovakia). Please refer to the sponsor's study report of HMAY(A) Appendix 16.1.3 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to determine the safety and efficacy of duloxetine 60 mg bid compared to placebo in the treatment of patients diagnosed with major depressive disorder.

Population

Patients chosen for this study were physically healthy adults at least 18 years of age diagnosed with major depression as defined by DSM-IV. Required for participation were HAMD₁₇ score ≥ 15 and CGI-S scores ≥ 4 at screening and baseline. Excluded from the study were patients with co-morbid Axis I diagnoses, a history of substance abuse/dependence, or a suicidal risk. Women of child-bearing potential were required to use medically approved forms of birth control. Patients who appeared to be treatment resistant (i.e. obtained 2 or more adequate trials of antidepressants) or were ever treatment resistant to trials of paroxetine were also excluded from the study.

Design

This was a randomized, multi-centered, double-blind, placebo and comparator (paroxetine) controlled study. The study began with a one week placebo-lead in, followed by 8 weeks of treatment, and concluded with a 26 week continuation phase for responders with a two week placebo lead out; all patients who continued into the continuation phase this phase remained in the same treatment group to which they were randomly assigned at the beginning of the study. At the beginning of the study, patients were randomized to one of the following groups: 1) placebo, 2) duloxetine 20 mg bid, 3) duloxetine 40 mg bid titrated over 3 days, 4) duloxetine 60 mg bid (titrated over 6 days), or 5) paroxetine 20 mg qd. Benzodiazepine and select hypnotics were permitted to be used for a total of 6 days during the acute phase of the study; otherwise, psychotropic medications were forbidden during the study.

Screening included a history and physical, ECG, routine labs, urinalysis, urine drug screen, thyroid function test, and pregnancy test (females). Vital signs were recorded weekly for the first month and then biweekly until week 8 of the acute phase; hematology and routine chemistry labs were repeated at the conclusion of the acute phase of the study. For the 26 week continuation phase, labs were monitored on a monthly basis. Post baseline ECGs were only recorded at the conclusion of the entire study or at early discharge.

Analysis Plan

The primary efficacy variable compares the endpoint of the HAMD₁₇ scores in the duloxetine 60 mg bid group compared to the placebo group in the acute phase of study after accounting differences in the baseline scores. Please refer to the statistics review by Ohidul Siddiqui for details of the primary efficacy analysis.

Secondary efficacy assessments included the SCI-S, MADRS, HAM-Anxiety, Arizona Sexual Experiences Scale (ASEX), Patient Global Impression of Improvement (PGI-Improvement), Somatic symptom Inventory (SSI), and Visual Analog Scales (VAS).

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 440 patients entering the screening phase of the study, 367 patients were randomized to one of the four treatment groups. Reasons for ineligibility included failure to meet entry criteria (n=45), adverse events (n=4), lack of efficacy (n=2), satisfactory response (n=1), personal conflict or other (n=4), physician decision (n=2), protocol violations (n=5). There were 318 patients who completed the acute treatment phase of the study of which 272 entered the continuation phase. The entire study was completed by 221 patients. Reasons for early withdrawal from the acute phase of the treatment included the following: adverse events, lack of efficacy, personal conflict, lost to follow up, sponsor's decision, protocol violation. Table 1 below elaborate on the percentages of patients who dropped out for each reason with the treatment groups.

Appendix Table A1 Reasons for withdrawal during the acute phase

	PLACEBO N=93	DLX 40BID N=95	DLX60BID N=93	PRX20QD N=86
Adverse events	3 (3.2%)	4 (4.2%)	3 (3.2%)	3 (3.5%)
Lack of efficacy	7 (7.5)	3 (3.2)	2 (2.2)	1 (1.2)
Personal conflict	2 (2.2)	4 (4.2)	3 (3.2)	3 (3.5)
Lost to follow up	2 (2.2)	0	0	3 (3.5)
Sponsor decision	3 (3.2)	1 (1.1)	0	0
Protocol violation	1 (1.1)	0	1 (1.1)	0

As would be expected, there was a higher percentage of patients who withdrew due to lack of efficacy compared to the other treatment groups. The follow table summarizes reasons for discontinuation from the continuation phase of the trial:

Appendix Table A2 Reasons for withdrawal during the continuation phase of the study

	PLACEBO N=58	DLX 40BID N=70	DLX60BID N=75	PRX20QD N=70
Adverse event	3 (5.2)	2 (2.9)	4 (5.3)	2 (2.9)
Death	1 (1.7)	1 (1.4)	1 (1.3)	0
Satisfactory response	0	4 (7)	2 (2.7)	4 (5.7)
Lack of efficacy	9 (15.5)	0	1 (1.3)	1 (1.4)
Lost to follow up	2 (3.4)	0	2 (2.7)	1 (1.4)
Personal conflict	2 (3.4)	3 (4.3)	1 (1.3)	0
Physician decision	0	0	1 (1.3)	0
Protocol violation	2 (3.4)	0	1	0
Total patients continuing	39 (67.2)	60 (85.7)	62 (82.7)	61 (87.1)

Demographics /Group Comparability

The majority of the patients in this study were Caucasian females. Participating in the study were 267 females (72.8%) and 100 males (27.2%). The mean age was 43 years old (Range 19 to 74). The treatment groups appears to be comparable at baseline for demographics and severity of illness.

Concomitant Medications

Concomitant medications were used by approximately 50 % of patients in the placebo and duloxetine groups, and by approximately 40 % by patients in the paroxetine. Concomitant medications were used more frequently in the duloxetine and placebo groups than in the paroxetine group. The sponsor did not provide details of concomitant medications used.

Efficacy Results

The sponsor was able to demonstrate a statistically significant result using a Repeated Measures Analysis (p=0.001 for duloxetine 40 mg bid group, and <0.001 for the duloxetine 60 mg bid and paroxetine 20 mg qd groups). Statistical significance was also seen using the mean change from baseline to endpoint (p=0.007 for duloxetine 40 mg bid group, and p<0.001 for duloxetine 60 mg bid). Please refer to the sponsor's tables below for the complete analysis. It is noted that there did not appear to be a statistically significant difference between the 40 mg bid group and the 60 mg bid group using either method of analysis.

Appendix Table A3 HAM₁₇ Total Score using Repeated Measures Analysis for Acute Treatment Phase (sponsor table HMAYa.11.5)

Therapy	Visit(Week)	N	LSMean	LSMean Change	SE	T	DDF	w/in p-Val	Pairwise p-Val		
									vs. 1)	vs. 2)	vs. 3)
1) PLACEBO	4 (2)	93	18.04	-1.98	0.30			<.001			
2) DLX40BID		93	18.58	-1.45	0.30	-1.26	387	<.001	.207		
3) DLX60BID		93	18.21	-1.82	0.30	-0.39	387	<.001	.697	.382	
4) PRX20QD		85	18.18	-1.85	0.32	-0.31	387	<.001	.754	.358	.946
1) PLACEBO	5 (3)	92	15.44	-4.58	0.42			<.001			
2) DLX40BID		90	15.59	-4.43	0.42	-0.25	377	<.001	.803		
3) DLX60BID		89	14.96	-5.07	0.43	0.81	378	<.001	.416	.290	
4) PRX20QD		82	14.88	-5.15	0.45	0.92	377	<.001	.357	.246	.900
1) PLACEBO	6 (5)	90	13.65	-6.37	0.48			<.001			
2) DLX40BID		88	13.16	-6.86	0.49	0.71	368	<.001	.479		
3) DLX60BID		87	11.42	-8.60	0.49	3.23	369	<.001	.001	.012	
4) PRX20QD		80	12.04	-7.98	0.51	2.28	369	<.001	.023	.114	.384
1) PLACEBO	7 (7)	84	12.36	-7.67	0.49			<.001			
2) DLX40BID		85	10.61	-9.41	0.50	2.50	365	<.001	.013		
3) DLX60BID		86	9.01	-11.02	0.50	4.79	364	<.001	<.001	.022	
4) PRX20QD		77	9.88	-10.14	0.52	3.46	366	<.001	<.001	.309	.224
1) PLACEBO	8 (9)	76	11.25	-8.78	0.50			<.001			
2) DLX40BID		85	9.02	-11.01	0.49	3.20	363	<.001	.001		
3) DLX60BID		84	7.94	-12.08	0.49	4.73	363	<.001	<.001	.122	
4) PRX20QD		76	8.35	-11.68	0.52	4.05	364	<.001	<.001	.347	.569

Appendix Table A4 HAM₁₇ Total Score Mean change from Baseline to endpoint Study HMAYa

TREATMENT	N	MEAN CHANGE	P-VALUE COMPARED TO PBO
Placebo (PBO)	93	-8.11	
Duloxetine 40 bid	93	-10.28	p=0.007
Duloxetine 60 bid	93	-11.32	p < 0.001
Paroxetine 20 mg	85	-11.06	p=0.001

Conclusions

This study provides evidence for the efficacy of doses of duloxetine 40 mg bid and 60 mg bid. It is noted that there was no statistically significant difference in the efficacy findings between these two treatment dose groups.

APPENDIX B
Study HMAY (B)

This was a 22 site (outside the USA), double blind, placebo and comparator (paroxetine) controlled study. The details of this study's design were identical to Study HMAY (A) (please refer to Study HMAY (A) above). Utilizing the Repeated Measures Analysis, the duloxetine groups appeared to have positive efficacy findings (for dlx 40 mg bid: p=0.045; and dlx 60 mg bid: p=0.014); however, the comparator (paroxetine) group did not have positive results (p=0.089), suggesting a failed study. Using the Mean Change from Baseline to Endpoint analysis, none of the treatment groups demonstrated statistical significance compared to placebo (duloxetine 40 bid: p=0.253, for duloxetine 60 bid: p=0.054, and paroxetine 20 mg: p=0.194) Please refer to the tables below for further details of the analysis.

Appendix Table B1 HAM₁₇ Total Score using Repeated Measures Analysis for Acute Treatment Phase (sponsor table HMAY.11.5) b9

Therapy	Visit (Week)	N	LSMean	LSMean Change	SE	T	DDF	w/in p-Val	Pairwise p-Val		
									vs. 1)	vs. 2)	vs. 3)
1) PLACEBO	4 (2)	99	18.66	-2.34	0.30			<.001			
2) DLX40 BID		93	19.07	-1.93	0.31	-0.98	412	<.001	.330		
3) DLX60 BID		102	19.24	-1.75	0.29	-1.44	412	<.001	.151	.664	
4) PRX20 QD		97	19.46	-1.54	0.30	-1.94	412	<.001	.053	.347	.600
1) PLACEBO	5 (3)	97	15.98	-5.01	0.38			<.001			
2) DLX40 BID		90	16.15	-4.85	0.40	-0.31	402	<.001	.757		
3) DLX60 BID		100	16.09	-4.90	0.38	-0.21	400	<.001	.835	.914	
4) PRX20 QD		94	16.22	-4.77	0.39	-0.45	402	<.001	.653	.894	.806
1) PLACEBO	6 (5)	97	13.09	-7.91	0.43			<.001			
2) DLX40 BID		89	13.47	-7.53	0.44	-0.63	391	<.001	.529		
3) DLX60 BID		97	12.69	-8.31	0.42	0.67	391	<.001	.503	.197	
4) PRX20 QD		89	13.10	-7.89	0.44	-0.03	395	<.001	.976	.554	.489
1) PLACEBO	7 (7)	94	11.35	-9.65	0.44			<.001			
2) DLX40 BID		85	10.88	-10.12	0.46	0.76	389	<.001	.450		
3) DLX60 BID		94	10.34	-10.66	0.43	1.66	387	<.001	.098	.388	
4) PRX20 QD		89	10.88	-10.12	0.45	0.76	387	<.001	.447	.998	.384
1) PLACEBO	8 (9)	92	10.22	-10.77	0.47			<.001			
2) DLX40 BID		85	8.86	-12.14	0.49	2.02	381	<.001	.045		
3) DLX60 BID		92	8.60	-12.40	0.47	2.46	382	<.001	.014	.698	
4) PRX20 QD		88	9.08	-11.92	0.49	1.70	380	<.001	.089	.746	.470

Appendix Table B2 HAM₁₇ Total Score Mean change from Baseline to endpoint Study HMAYb

TREATMENT	N	MEAN CHANGE	P-VALUE COMPARED TO PBO
Placebo (PBO)	99	-9.99	
Duloxetine 40 bid	93	-11.54	p=0.253
Duloxetine 60 bid	102	-11.72	p=0.54
Paroxetine 20 mg	97	-10.84	p=0.194

Conclusions

As can be seen from above, HMAYb appears to be a failed study, and does not provide evidence support to the efficacy of duloxetine for the treatment of depression.

Appendix C

Mean Changes in Blood Pressure with Duloxetine Treatment in the Placebo Controlled Primary Safety Database (extracted from review by Paul Andreason, M.D. 8/16/02)

Variables	Therapy	n	Mean	SD	Mean Change	SD
Systolic BP						
	Standing					
	Placebo	138	117.870	12.990	-0.754	10.086
	Duloxetine Forced Titration	149	119.322	14.651	1.611	11.783
Supine	Placebo	698	120.497	13.672	-1.372	12.059
	Duloxetine 20-mg bid	305	119.357	13.937	0.210	12.435
	Duloxetine 60-mg qd	244	122.090	13.135	0.344	12.527
	Duloxetine 40-mg bid	299	119.946	13.643	2.344	13.183
	Duloxetine Forced Titration	149	121.732	13.786	2.295	11.787
Diastolic BP						
	Standing					
	Placebo	138	76.746	9.095	-0.428	7.994
	Duloxetine Forced Titration	149	78.208	8.962	1.470	8.538
Supine	Placebo	698	74.903	9.998	0.175	8.809
	Duloxetine 20-mg bid	305	74.882	8.884	1.275	8.456
	Duloxetine 60-mg qd	244	75.152	9.624	1.299	9.922
	Duloxetine 40-mg bid	299	76.304	9.128	1.318	8.414
	Duloxetine Forced Titration	149	76.510	8.815	1.644	8.752

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/s/

Roberta Glass
9/10/03 09:39:32 AM
MEDICAL OFFICER

Paul Andreason
9/15/03 02:07:06 PM
MEDICAL OFFICER
Please see memo to file.

Review and Evaluation of Clinical Data
Safety Team Leader Review of Selected Safety Issues in the
Response to Approvable Letter

NDA: 21-427
Drug: duloxetine (CYMBALTA)
Route: oral
Indication: major depressive disorder
Sponsor: Lilly
Action Date: 9/25/03

Background

Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, is indicated for the treatment of major depressive disorder (MDD). \perp

During the recently completed first cycle review of duloxetine. \perp

\perp the safety issue of hepatotoxicity became prominent.

Additionally, drug-drug interaction studies performed after the first cycle review for MDD identified that there was a potential for patients to be exposed to high serum levels of duloxetine- levels at which the effect on cardiac repolarization (as measured by the QT interval) have not been fully characterized. This memo will review the hepatotoxicity and QT prolongation issues.

Hepatotoxicity

DNDP 1st cycle review

In Dr. Paul Andreason's clinical first cycle review of duloxetine, he noted that there were small but statistically significant mean increases in the AST (1.7 U/L), ALT (1.4 U/L), and alkaline phosphatase ([AP] 1.4). The analysis of treatment emergent abnormal values (threshold not indicated in the review) at anytime during the study indicated about a three-fold excess in the duloxetine group (2% [19/941] vs. 0.6% [4/664]).

The approvable letter for duloxetine, dated 9/13/02, had the following request:

"We have also identified two patients, A09505 and E00301, who had abnormal liver chemistries identified as serious adverse events. Please provide more complete details on these cases, including information on concomitant medications, co-morbid conditions, and more complete follow-up information. Labeling may need further revision based on whatever information can be obtained."

DNDP 2nd cycle review

In their submission dated 3/24/03, Lilly responded to the request from the approvable letter for duloxetine shown above. They included liver-related adverse event summaries for patients A09505 and E00301, as well as other patient summaries thought to be relevant to the hepatotoxicity issue. The summaries for patients from Japanese studies are based on translated case report forms and personal conversations with representatives [redacted], and the owners of the databases containing these patients. Lilly representatives went to Japan, but did not have direct access to investigators or source documents.

Cases requested in by DNDP in AE letter

Subject A09505 (study 321G) was a 30 yo Asian male who experienced the SAEs of elevated ALT and bilirubin. The patient had a history of ingesting 1.5L/day of ethanol at study entry. Baseline GGT was elevated at 215 IU/L (nl 6-60), baseline AP was at the upper end of the normal range (237, nl range 80-240), but ALT, AST, and TB were within normal limits. The patient initially took 10 mg/ day of duloxetine, but about one month into the study was taking 30-40 mg/day. At about the same time, the patient began taking other medications prescribed at another institution including alprazolam, flunitrazepam, brotizolam, fluvoxamine, trazodone, and Vegetamin D (active ingredient not specified). The narrative also states “he was *presumed* (italics my emphasis) to be drinking large amount of alcohol but no actual information about the extent of his drinking during this period is available.” Due to the protocol violation of taking the other prescription medications, duloxetine was discontinued two weeks after starting the other medications. The patient’s LFTs over the course of the trial are summarized below.

Pertinent lab values A09505 (study 321G)

Date	ALT	AST	AP	GGT	Total Bilirubin
(baseline)	18	29	237	215	0.4
	37	33	296	215	0.7
9/21/00 (duloxetine discontinued)	2362	2837	454	497	2.3
	455	62	388	432	1.0
	55	23	268	308	1.1

Serologies for viral hepatitis were negative. The patient was diagnosed with “suspected drug hepatopathy”, but was not hospitalized due to an absence of signs and symptoms. Follow-up labs ten days later showed substantial improvement in the LFTs.

Reviewer comment

Although the ALT and TB abnormalities meet the threshold for serious liver injury, the interpretation of this case is confounded by several issues including an abnormal baseline elevation of GGT and a rising AP prior to the transaminases “bump”, the initiation of five new drug products two weeks prior to the transaminases “bump”, and the possibility of concurrent ethanol abuse (although the sponsor report seems more speculative than

evidence-based on this issue). Additionally, the sponsor draws attention to the rapid fall in transaminases over a four day period which, while not impossible, is unexpected.

Subject E00301 (study 324G) was a 73 yo Asian male who experienced the SAEs of elevated total bilirubin, tremor, and abnormal ECG. The patient started treatment with duloxetine on 2/26/00, one day after being discontinued from fluvoxamine, bromazepam, alprazolam, triazolam, nitrazepam, trazodone, and flunitrazepam. He was also taking bromhexine, a combination vitamin product with C, B12, and riboflavin, a formulation of parotin (a gastrointestinal hormone commonly taken by men in Asia to promote potency), and Chistanin (the sponsor was unable to identify the active product in this agent). On [] the patient experienced a “general convulsion like tremor”. He was hospitalized on [] and duloxetine was stopped. Reportedly the patient had poor nutritional status (6 kg weight loss over two weeks) and dehydration from anorexia and insomnia. The liver-related abnormalities are summarized below.

Pertinent lab values E00301 (study 324G)

Date	ALT	AST	AP	GGT	Total Bilirubin
(baseline)	36	27	188	21	0.4
(duloxetine discontinued)	47	25	211	25	1.4
--	21	16	141	Not done	0.3

Following duloxetine discontinuation, the patient’s appetite improved and the LFT abnormalities resolved.

Reviewer comment

Although the patient’s LFT abnormalities resolved after duloxetine discontinuation, they never reached the threshold of serious liver injury. The changes may have been related to intercurrent rapid changes in nutritional status.

Additional cases of severe liver injury submitted by Lilly

The sponsor’s submission included four additional cases of hepatotoxicity; two occurring in duloxetine-treated patients, and two occurring in placebo patients. Dr. Zili Li, of DRUDP, described the two duloxetine-associated cases in great detail in his review. A tabular summary of patients 500-5254 (HMAW) and A06706 (321G), along with A09595 (see above), follows below in the “DRUDP 1st cycle review” findings section below. However, Dr. Li did not summarize the placebo cases. I will briefly describe these four patients below.

Duloxetine Treated

Subject 500-5254 (HMAW): This was a 43 yo male with history of diabetes and ethanol abuse who was treated with duloxetine for DN. He had been on metformin for 8-10 years. After approximately 12 weeks of 60 mg/d of duloxetine in the RCT, he entered the open label portion of the trial, and his dose increased to 60 mg BID. After about eight weeks of BID treatment, the patient went on a drinking binge. About three weeks later, the patient noticed jaundice, and was discontinued from duloxetine about one week after that (L 3) after about 6.5 months on duloxetine). The patient was hospitalized on L 3 for assessment of jaundice. Note that the patient's AP and GGT had been fluctuating prior to the episode of severe liver injury.

Pertinent lab values 500-5254 (HMAW)

Date	ALT	AST	AP	GGT	Total Bilirubin
(baseline)	31	33	87	68	0.9
(last value on 60 q d)	20	27	131	114	0.9
(on 60 BID for 2 mos)	28	26	149	92	1.1
(on 60 BID for 3 mos)	37	44	115	159	0.4
	475	427	1296	500	13.7
		68	290		29.3
	42	85		136	19.5
	28	38	164	120	3.7
	22	29	154	98	1.2
	22	36	127	276	1.1

Several tests looking for an etiology were negative including viral serologies, autoimmune panel, and alpha fetoprotein. The abdominal US showed ascites, a CT showed hepatosplenomegaly and fatty liver, and laboratory tests showed prolonged INR (1.25 on L 3), reduced serum albumin, target cell anemia, and thrombocytopenia (all signs of decompensated liver disease). Note: the accompanying laboratory data sheet showed low platelets on L 3 (124K down from 240K in L 3, but no albumin value was reported for the period corresponding to the episode of serious hepatic injury (it was normal in L 3). A liver biopsy was performed and reviewed by multiple hepatologists. The biopsy slides showed "severe fibrosis...a modest inflammatory response and hepatocellular injury with severe cholestasis." No clear etiology was implicated. The sponsor's hepatologist consultant, L 3, suggested that the pattern was not consistent with pure alcoholic hepatitis ("acute alcohol injury"), but it suggested the presence of underlying liver disease prior to the study. L 3 also suggested a work-up for sarcoid because of two granulomas seen on the biopsy. The

sarcoid work-up revealed an ACE level of 134 (nl 9-63) and a few non-specific nodules in the RLL and LLL on a chest CT. The sponsor interpreted these findings as being consistent with acute sarcoidosis. Within a few weeks after the duloxetine and the binge drinking stopped, the transaminases resolved; however, the TB normalized more slowly (Table 1). Notably, in Table 2 the GGT began to rise again. No more recent labs are presented.

Reviewer comment

The patient clearly suffered a severe liver injury, but multiple confounding factors are present. First are the history of alcohol abuse and the drinking binge immediately prior to the liver decompensation, although the liver biopsy was not consistent with an “acute alcohol injury”. We don’t know about other potential ingestions such as acetaminophen, or about the possibility of ethanol potentiating a duloxetine-related injury. Secondly, there is the possibility of active sarcoidosis producing or exacerbating the liver injury. Thirdly, the patient’s AP and GGT had been fluctuating prior to the acute decompensation such that the case is not consistent with the strict definition of Hy’s law. Finally, the GGT began to rise again several months after duloxetine discontinuation, suggesting some ongoing hepatobiliary process.

Subject A06706 (study 321G): This was a 45 yo Asian male enrolled in an open label trial of duloxetine for MDD. The patient had a history of ethanol abuse, drinking approximately 700 ml of beer each day. Signs of chronic ethanol use included macrocytosis with normal hemoglobin and decreased folic acid levels at baseline. The patient reported a history of abnormal LFTs at another hospital prior to study initiation. The patient took duloxetine 10 mg/day for two weeks, followed by 20 mg/day for two weeks, and then increased to 30 mg/day. Over the next two months the patient did not come in for regular study visits, and the investigator suspected that the patient increased his drinking and self-medicated with nortriptyline that he had at home. For personal reasons, the patient began taking duloxetine sporadically and increased his drinking “dramatically”, coming to study visits smelling of ethanol. In early Table 1 the physician decreased the daily dose to 20 mg/day. One month later in early Table 2 he further decreased the dose to 10 mg/day because he thought the patients labs suggested alcoholic hepatitis. Also, the physician prescribed zopiclone for sleep at this visit. The patient completed the trial on 3/31/03.

Pertinent lab values A06706 (study 321G)

Date	ALT	AST	AP	GGT	Total Bilirubin
(baseline)	35	52	385	103	0.6
(20 q d)	28	40	226	74	0.9
(30 q d for 2 mos)	16	30	234	31	0.4
	53	91	308	123	1.4

(30 q d for 4 mos)					
(10 q d for 2 weeks)	528	816	400	401	2.9
3/31/03 (10 q d for 4 weeks, end of study)	161	275	548	533	1.4

A hepatic US on [] showed an enlarged fatty liver, a dull echo from the liver edge, a smooth liver surface, no dilation of intrahepatic bile ducts, no stones, a thickened gall bladder wall, no dilation of the common bile duct, and no pancreatic abnormalities.

Reviewer comment

The investigator considered this case to be consistent with alcoholic hepatitis, given the patient's drinking history and the liver ultrasound results. AP, GGT, and AST were abnormal at baseline, suggesting some pre-existing liver pathology. The patient's severe liver injury appeared to be associated with a substantial increase in drinking, and resolved while the patient was on duloxetine, although at a reduced dose. The potential role of duloxetine in potentiating liver injury can not be ruled out; however, this is not a clean "Hy's law" case.

Placebo Treated

Subject 120-3017 (HMBH): This was an 83 yo Caucasian male treated with placebo in a MDD study. His baseline labs were reported to be normal (although the exact values were not provided in the summary). Forty-nine days into the trial the ALT was 130 (nl 6-35), AST 87 (nl 11-36), and TB 2.5 (nl 0.2-1.2). No work-up for these abnormalities is described. One month later the abnormalities had resolved. No treatment-emergent AEs were reported around the time of the lab abnormalities. Concurrent medications were naproxen, ranitidine, glucosamine, aspirin, vitamins, calcium, and Metamucil reportedly taken throughout the trial.

Reviewer comment

Because there is only one set of abnormal lab values, it is difficult to assess whether this was a real transient liver injury, or a lab error. NSAIDs are commonly associated with drug-induced hepatitis, but the history suggests that this medication was longstanding. It seems strange that the development of these abnormal labs in an 83 year old did not stimulate the investigator to refer the patient for a liver work-up. Additional information about this patient will be requested from the sponsor.

Subject 606-6602 (HMBC): This 41 yo Caucasian male participating in a MDD study had normal transaminases and an abnormal TB of 1.4 at baseline. The patient took duloxetine 60 mg/day for 12 weeks in an open phase of the trial; LFTs from this period were not reported in the case narrative. Five weeks into the placebo period, the TB

increased to 2.2 and the ALT increased to 405 (nl 6-43). Fractionation showed an unconjugated hyperbilirubinemia, although the fractions were not reported. Viral serologies were negative. Concomitant medications were vitamin C and Actifed. At the last visit the TB and ALT were “resolving”.

Reviewer’s comment

While Gilbert’s syndrome could have explained the hyperbilirubinemia, it does not explain the transaminitis. Again, a paucity of lab data makes it difficult to rule out a lab error. It seems strange that the development of these abnormal labs, especially the high ALT did not stimulate the investigator to refer the patient for a liver work-up. Additional information about this patient will be requested from the sponsor.

Sponsor’s Assessment

Lilly summarizes that 8604 patients have been exposed to duloxetine in the development programs for MDD, DUI, DN, \downarrow (7545 in Lilly trials and 1059 in \downarrow trials). In those development programs, 2867 patients have been exposed to placebo.

Among duloxetine patients, they conclude that one [500-5254 (HMAW)] met Hy’s rule in clinical presentation and laboratory measures ($1/8604=0.01\%$), and two met the laboratory criteria ($2/8604=0.02\%$). At the same time, two placebo treated patients met the laboratory criteria ($2/2867=0.07\%$). Although the sponsor purports that the placebo patients’ liver injuries were of a different quality than those of the duloxetine-treated patients, their occurrence suggests that important elevations of transaminases and TB do occur in the background population.

In addition to the specific case mentioned above, Lilly’s hepatology consultant, \downarrow reviewed the full complement of liver-related data from the duloxetine development program. His conclusion, in a letter dated 3/7/03, is summarized below:

- Hepatotoxicity can be seen with duloxetine
- It is not certain if the three severe duloxetine-associated cases (described above) were truly duloxetine hepatotoxicity, nor whether prior and concomitant alcohol abuse contributed to liver damage
- If the hepatotoxicity is due to duloxetine, then the incidence of severe liver injury is about 1/3000, implying an incidence of liver failure of about 1/30,000 (he then qualifies this estimate because the “denominator is small” and two of the cases had a TB only around 2-3)
- Perhaps abstinence from alcohol may modify the number of severe cases

DRUDP 1st cycle review (including ODS consultant review)

Review Findings

Dr. Zili Li, of DRUDP performed a detailed analysis of the liver-related AEs and laboratory values in the combined SUI laboratory database, as well as the database combining MDD and diabetic neuropathy (DN) trials (see pp. 60-70 of his review dated

8/29/03). In the combined SUI database, the percent of subjects with a ALT of 3X ULN post baseline in the duloxetine group was 1.3% (11/792) compared with 0.2% (2/808) in the placebo group. The p-value is significant at $p = 0.01$ level. There was no excess frequency of abnormal total bilirubin (TB) among duloxetine users compared to placebo patients. In the combined database of six controlled MDD and DN trials, the percent of subjects with a ALT of 3X ULN post baseline in the duloxetine group was 1.0% (5/502) compared with 0% (0/513) in the placebo group. There was no excess frequency of abnormal TB among duloxetine users compared to placebo patients.

Dr. Li also described patients who had evidence of marked liver injury as evidenced by ALT elevations of >10x ULN alone or in combination with abnormal TB values. Duloxetine-treated patients from controlled trials (n=2) and open label extensions (n=1) who did not have substantial change in TB associated with their transaminases elevations are described below:

Subject 120-3009 (Study SBAV) had an ALT peak of 354 associated with a TB peak of 0.7 (increase from baselines of 17/0.5, respectively) and a normal AP about two months into duloxetine treatment. The subject discontinued and had a follow-up ALT/TB two weeks later that showed normalizing of the ALT (57/0.7).

Subject 105-1523 (Study HMBO) had an ALT peak of 543 associated with a TB of 0.5 (increase from baselines of 15/0.3, respectively) and a normal AP 56 days into duloxetine treatment. The subject discontinued four days after the measurement of the peak ALT. The TB peaked at 0.7 about 11 days later, associated with a falling ALT (229). Follow-up ALT/TB two months later that showed a return of the ALT and TB to baseline (13/0.3).

Subject 114-6708 (SBAW) had an ALT peak of 361 associated with a TB of 0.2 (increase from baselines of 15/0.2, respectively) and a normal AP about six weeks into duloxetine treatment. The subject continued on therapy. The TB peaked at 0.3 about one week later, associated with an ALT of 349. Follow-up ALT/TB two weeks later that showed a falling ALT towards baseline (132). ALT normalized about one month later (40).

Three additional patients showed evidence of transaminase elevation greater than 3x ULN, combined with abnormal TB. These three patients' histories and lab values are described above in the DNDP 2nd cycle review section. Dr. Li's table summarizing the salient characteristics of these three patients follows below:

Table VII-C-9.4 Summary of demographic and clinical information of three subjects who experienced an abnormal ALT and hyperbilirubinemia while being treated with duloxetine

Patient Number	500-5254	A09505	AO6706
Study	FIJ-MC-HMAW (pain)	FIJ-JE-321G (depression)	FIJ-JE321G (depression)
Age	43	30	45
County	Canada	Japan	Japan
Sex	Male	Male	Male
Dose of duloxetine	60 QD/BID	10 – 40 mg QD	10-30 mg QD
Date of first dose	21 Jan 2002	11 Aug 2000	31 Aug 2000
Onset of liver injury	24 weeks	6 weeks	20 weeks

Liver failure	None	None	None
Hospitalization/death	Yes/No	No/No	No/No
Jaundice	Yes	No	No
Peak ALT/AST/Bili	475/427/29.3	2,362/2,837/2.3	528/816/2.9
Discontinuation of drug	Yes	Yes	No but the dose was reduced
Length of liver injury	2-4 months	16 days	> 1 month
Liver biopsy	Fibrosis but not consistent with alcoholic hepatitis	None	None
Lab tests			
Hepatitis	Negative	Negative	--
Alpha fetoprotein	Negative	--	--
Autoimmune disease	Negative	--	--
Suggested Contributing Factors			
Alcohol abuse	Yes	Yes, 1.5 L/day	Yes, 0.7/L day
Others medications		Yes, Trazodone	
Sarcoidosis	Yes		

HFD-580 obtained formal input from Office of Drug Safety hepatology consultant John Senior, MD (see review dated 7/31/03) regarding the potential hepatotoxicity with duloxetine. Dr. Senior's conclusion follows below:

- "Duloxetine, perhaps like its predecessor compounds fluoxetine and paroxetine, may occasionally cause drug-induced hepatotoxicity in a few persons taking recommended doses...In several individual cases, more severe liver injury was seen in patients taking both duloxetine and excessive amounts of ethanol, but it was not clear if alcohol aggravated duloxetine-induced effects or vice versa. From these three cases, it may be concluded that the combination of duloxetine and excessive ethanol should be avoided and this should be reflected in the labeling."

Dr. Senior raised the concern about the potential for concurrent use of ethanol and duloxetine and made the following recommendations related to that concern:

- advise against administering duloxetine to patients who are or may be likely to be abusing ethanol, and also advise those taking duloxetine not to drink or to do so very lightly
- carry out studies in at least one rodent and non-rodent species to assess the combined effects of duloxetine and excess ethanol administration, with dose ranging and serial serum enzyme monitoring, with histological data

DRUDP requests in the approvable (AE) letter for duloxetine regarding the liver

DRUDP included several requests in their AE letter for duloxetine (dated 8/29/03) to further elucidate the hepatotoxic potential of duloxetine. The requests (paraphrased) follow below:

- Updated outlier analysis for important elevations of transaminases, with and without bilirubin elevation from ongoing clinical trials in any indication
- Narrative summaries for patients identified in the outlier analyses
- In vitro studies to assess the potential mitochondrial toxicity of duloxetine and its major human metabolites
- A study to evaluate the *in vivo* interaction of ethanol with duloxetine in an appropriate animal model
- An *in vitro* dissolution study of the product's enteric coating, due to the possible formation of 1-alpha-naphthol, a hepatotoxin

Recent sponsor submitted severe liver injury case

In a submission dated August 15, 2003, Lilly provided a MedWatch report describing severe liver injury in a patient being treated with duloxetine in an ongoing clinical trial for diabetic neuropathy.

Briefly, subject 305-3512 (Study HMBT), a 60 year old Hispanic female with a medical history significant for diabetes mellitus, hypertension, and hyperlipidemia; and a surgical history significant for a partial colectomy for colon cancer (1999) and cholecystectomy (2000), received duloxetine for DN. About 4.5 months into therapy the patient experienced epigastric pain, fever and nausea for two days. The patient's pertinent lab values are summarized below. Reportedly the patient's lab values returned to normal except for a new increase in GGT and lipase (values and dates not reported).

Date	ALT	AST	AP	GGT	Total Bilirubin
(baseline)	27	27	71	51	0.4
	19	13	55	25	0.4
	41	136	128	588	1.9
4/21/03	Duloxetine discontinued (pt reportedly took no dose that day)				
	90	34	84	266	0.5

A liver ultrasound (date performed not provided) showed a "normal biliary pathway and neither residual (or recurrent) choledochus lithiasis nor macroscopic abnormalities in the pancreas". A local specialist thought there might be a common bile duct stone that may have migrated. The sponsor's consultant gastroenterologist concluded that "the possibility of residual microlithiasis, biliary colics, and pancreatic repercussions persists...the possibility of a focal hepatic lesion has been reasonably ruled out based on the ultrasound." The episode of abdominal pain was attributed to the possibility of surgical adhesions. Finally, the consultant noted that "non-alcoholic hepatic steatosis associated with diabetes and hypertriglyceridemia has been confirmed by ultrasound," and stated that the high GGT levels were consistent with this.

Dr. John Senior of ODS also reviewed this case report. His assessment was that the high GGT in association with no alkaline phosphatase elevation was evidence against the passage of a common bile duct stone. He theorized that the GGT could be consistent with

with elevated TB, however, had concurrent transaminases abnormalities (see section 2.4.11.1.1).

Section 2.4.8.2 mentions a patient on **blinded** therapy with elevated AST, ALT, and alkaline phosphatase, stating “the subject’s pretreatment values were normal, increased on treatment to 52, 93, & 151, seven days after stopping study drug were 148, 393, & 485. The sponsor provided no information about bilirubin results, diagnostic workup or outcome of this event.”

I re-examined the NDA safety review (performed by Drs. David Gan, Gerard Boehm, Greg Dubitsky, and myself) for evidence of serious liver injury; about 1000 patients were exposed in the controlled trials. The “Gastrointestinal” section of the “Review of Systems” notes “No liver failure or hepatitis was reported”. The laboratory section does not describe any abnormalities related to liver enzymes.

Reviewer comment

Re-examination of the reviews of three recently reviewed NDAs for psychotropic drugs did not reveal the frequent occurrence of liver injury attributed to ethanol use. As such, it is difficult to interpret the three cases of severe liver injury in the duloxetine NDA safety database associated with ethanol use as being within the norm for psychotropic drug NDAs. It should be noted, however, that each of the re-examined safety databases were substantially smaller than that of duloxetine.

Transaminase elevations in clinical development programs

In a memo dated 5/6/99 evaluating the risk of hepatotoxicity of nefazodone, Dr. Jerry Boehm summarized the data from the NDA reviews of recently approved antidepressants to determine if other antidepressants were associated with an excess in transaminase outlier risk. Only mirtazapine had a statistically significant difference for transaminase or TB outliers¹. Citalopram, sertraline, fluoxetine, and venlafaxine had relative risks for outliers at least 1.5x greater than placebo, but had p values >.05. Dr. Boehm’s conclusion from this analysis follows below:

- “Considering the percent with outliers and the relative risks, I do not find evidence of a substantial difference in risk for outliers for nefazodone compared to the other approved antidepressants. Many of these agents demonstrate increase in outlier risk and the inability to find statistically significant differences may be due to a lack of power. Differences in trial design, monitoring, and populations could have an impact on these comparisons and therefore limit any conclusions. In addition, it is not clear that short-term trials are of sufficient length to include the period of risk associated with hepatic injury, if one exists.”

¹ Nefazodone also reached statistical significance, but the laboratory data summary included studies that had not been included in the NDA safety database.

Reviewer discussion

As demonstrated in the outlier analyses from the SUI studies, as well as the MDD and DN studies, duloxetine appears able to cause important elevations of ALT (>3x ULN) over and above that observed in the placebo group. A small number of cases have demonstrated evidence of more severe transaminase elevations (>10x ULN). The degree of transaminase elevation in the controlled trials is on par with those observed in the short-term randomized controlled trials of the antidepressant mirtazapine. In that pool of studies, 1.9% [8/424] of mirtazapine-treated patients in clinical trials developed ALT >3x ULN compared with 0.3% [1/328] of placebo treated patients. In the NDA review of mirtazapine, no cases were described that met the Hy's law thresholds; one patient did have an ALT >10x ULN. Mirtazapine is labeled with a Precautions statement describing the transaminase elevation.²

Additionally, a small number of cases in duloxetine-treated patients have demonstrated severe transaminase elevations in combination with elevation of total bilirubin. None of these severe liver injury cases are unconfounded, however. As mentioned above, "Hy's law" refers to the observation made by hepatologist Dr. Hy Zimmerman that a substantial increase in serum transaminases (operationalized as >3x ULN) combined with an abnormal TB (operationalized as >2 mg/dl), a sign of impaired liver function, suggests the ability of a drug to cause severe liver injury; about 10% of cases would manifest as acute liver failure. Four cases described above meet the "Hy's Law" thresholds for transaminase and TB abnormalities; however, further examination of the laboratory profiles demonstrates that there were coincident abnormalities of alkaline phosphatase in three of the cases (present at baseline in cases AO9505 and AO6706). In the presence of other LFT abnormalities such as elevated alkaline phosphatase, the predictions of Hy's Law are not as easily applied.

Intercurrent ethanol abuse was an important factor in two, and possibly three, of the cases of severe liver injury. An examination of the reviews of three recently reviewed psychotropic NDAs, including about 4000 drug-treated patients, did not show evidence of frequent ETOH-related liver injury. Because SAEs occurring in placebo patients may not be described in detail in an NDA review, it can not be known for certain that there were no liver-related SAEs in the placebo treated patients in these safety databases. Based on this examination, I conclude that the observation of hepatotoxicity in heavy users of ethanol is not a common occurrence in the typical psychotropic NDA database. It should be noted, however, that the development program for duloxetine exposed a substantially larger number of patients than the databases examined.

² Transaminase Elevations: Clinically significant ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to REMERON® in a pool of short-term US controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued REMERON® treatment. REMERON® should be used with caution in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

The LFT abnormalities in the most recently reported case have been attributed by the sponsor to the passage of a common bile duct stone. Although it is not clear that is the etiology, it does appear that the LFT abnormalities normalized to a great extent while the patient was still on drug. While the potential role for duloxetine in causing the hepatotoxicity in each of these four cases can not be ruled out, there are no “clean” cases in which duloxetine is the only suspected causative agent.

Furthermore, there are two reportedly asymptomatic placebo patients who had lab values that met the Hy’s law criteria. These placebo patients are inadequately described; no effort appears to have been instituted to work-up these patients for their LFT abnormalities. However, their occurrence suggests that severe liver injury occurs at some measurable rate in the background unrelated to study drug use.

Conclusions and Recommendations regarding Hepatotoxicity

Duloxetine can cause hepatotoxicity in the form of transaminase elevations. It may also be a factor in causing more severe liver injury, but there are no cases in the NDA database that clearly demonstrate this. Use of duloxetine in the presence of ethanol may potentiate the deleterious effect of ethanol on the liver.

1. Placement of a Precautions statement describing the transaminase abnormalities and cases of severe liver injury associated with the combination of duloxetine use and ethanol abuse
2. Request that the sponsor provide close monitoring of the postmarketing experience of duloxetine with regard to liver AEs
 - a. Sponsor will be asked to expedite reporting of all liver-related AEs received during the postmarketing period
 - b. Sponsor will be strongly encouraged to provide extensive detailed follow-up on reported cases; cases that are poorly documented will be considered related to the drug until the sponsor shows otherwise
 - c. Sponsor will be asked to provide quarterly summaries on all liver related AEs along with an estimate of drug usage for that quarter and an explanation of the method used to estimate drug usage
 - d. DNDP, along with the Office of Drug Safety, will review the submitted data
3. In the event that unconfounded cases of severe liver injury or acute liver failure related to duloxetine treatment are identified and submitted early in the postmarketing period, the division will use the threshold of three “clean” cases to initiate additional regulatory action that could range from a more prominent warning to the withdrawal of the drug product.
4. The sponsor should provide any additional information on the severe liver injury cases that occurred in the two placebo patients.

QT interval assessment

DNDP 1st cycle review

Dr. Linda Fossom, DNDP pharmacology/toxicology reviewer, identified no evidence from the preclinical cardiac studies of a signal of a prolonging effect of duloxetine on cardiac repolarization.

In Dr. Andreason's clinical review of the duloxetine NDA (dated 8/19/02), he described the findings of the QT analyses on pp. 40-43. A total of 89 patients in seven phase I multidose PK studies of duloxetine were exposed to doses ranging from 20 mg BID to 60 mg BID. A plot of QTc (Fridericia) vs. duloxetine plasma concentration based on these studies suggested an inverse relationship (decreased QTcF with increased plasma concentration).

Mean change in QTcF from baseline to endpoint in the phase III controlled trials HMAT (a and b) showed a more negative value for the duloxetine group (n=143) than placebo (n=75) [-2.7 vs. -0.8]. The results were not broken out for the two duloxetine doses studies (20mg BID and 40 mg BID). No patients in these controlled studies met the sponsor's outlier criteria (>450 msec for men, >470 msec for women, with an increase of >30 msec from baseline). However, two women from the open label trial (n=127) met outlier criteria (488 msec [from 431 baseline] and 467 msec [from 423 baseline]).

Dr. Andreason concluded that "There is no indication that duloxetine leads to clinically significant changes in ECG or risk of a serious arrhythmia."

DRUDP 1st cycle review

Duloxetine is extensively metabolized by cytochrome P450 isozymes 1A2 and 2D6. Dr. Ron Kavanaugh, DNDP OCPB reviewer on the first duloxetine review cycle, noted that inhibition of 2D6 (by 20 mg of paroxetine) increased exposure by about 1.6-fold (review dated 8/23/02). Since the time of DNDP's first cycle review, the sponsor conducted and presented the findings of the metabolic inhibition studies for CYP1A2. Fluvoxamine was used to inhibit CYP1A2. DRUDP OCPB reviewer Christy Johns summarized the results of the study:

- Fluvoxamine significantly affected the pharmacokinetics of a single oral 60 mg dose of duloxetine. The mean AUC was increased 5.6-fold and the C_{max} was increased 2.4-fold. Duloxetine t_{1/2} was increased approximately 3-fold. Fluvoxamine had the same effects on the major metabolites of duloxetine.

The results of this study raised the concern for DRUDP that the QT interval had not been adequately assessed at serum levels potentially attainable with maximal inhibition of CYP1A2 and 2D6. The fluoroquinolones are inhibitors of CYP1A2. This interaction is

particularly important for patients being treated for SUI because these patients may develop urinary tract infections that may be treated with fluoroquinolones.

As such, Dr. Zili Li did a thorough review of the phase I and phase III studies in which the QT was measured to look for an effect of duloxetine on the QT interval at the doses intended for use and at doses approaching the expected serum levels with maximal metabolic inhibition.

Phase III data

The table below, taken from Dr. Li's review, summarizes the QT analyses (Fridericia's and Bazett's corrections³) from the pooled phase III SUI trials.

Table VII-C-8.2.1 Summary of QTc statistics from phase 3 clinical development program of SUI – a pooled analysis of three SUI pivotal trials

Measurement	Duloxetine (80 mg/day total, given as 40mg BID)	Placebo
Number randomized (N)	818	817
(1) QTcF (number and percent in the analysis)	738 (90%)	763 (94%)
Baseline (ms)	414.1	414.9
Change from baseline (ms)		
Mean	-1.4	1.7
Median	-1.1	1.4
Max		
Number and percent with QTc change \geq 30 ms	16 (2.2%)	26 (3.4%)
Number and percent with QTc change \geq 60 ms	2 (0.3%)	5 (0.7%)
Number and percent with QTc \geq 450 ms	32 (4.2)	34 (4.3%)
Number and percent with QTc \geq 480 ms	1 (0.1)	2 (0.3%)
Number and percent with QTc \geq 500 ms	0 (-)	2 (0.3%)
(2) QTcB (number and percent in the analysis)	738 (90%)	762 (94%)
Baseline (ms)	422.1	422.6
Change from baseline (ms)		
Mean	2.0	0.9
Median	2	1
Max		
Number and percent with QTc change \geq 30 ms	39 (5.3%)	34 (4.5%)
Number and percent with QTc change \geq 60 ms	2 (0.3%)	6 (0.8%)

³ Duloxetine causes about a 3-4 beat per minute increase relative to placebo, so Fridericia's is probably the more accurate correction to use. Bazett's correction could cause an artifactual prolongation in a drug that causes tachycardia.

Number and percent with QTc \geq 450 ms	89 (11.7%)	73 (9.4%)
Number and percent with QTc \geq 480 ms	7 (0.9%)	7 (0.9%)
Number and percent with QTc \geq 500 ms	0 (--)	1 (0.1%)

Source Data: ecg.xpt file for three pivotal trials.

Stata programs used: AE#07 – ECG.DO and ANA #07 – ECG.DO

As can be seen in the table, at 40 mg BID, the dose intended for treatment of SUI, there was a negative mean change from baseline for QTcF and no difference from placebo in outliers. The results seen in this table provide some reassurance that at the dose intended for treatment of SUI, no signal of QT prolongation was observed. As with most clinical trials, though, the method of obtaining ECGs (usually coinciding with the time of the patient's visit) may not be the most sensitive for picking up a signal of QT prolongation.

Phase I data

In the Phase I program, the sponsor did a number of studies that assessed the ECG at different doses and times relative to baseline. The table below, taken from Dr. Li's review, summarizes the salient features of these phase I trials.

Table VII-8.1 List of duloxetine Phase 1 PK/PD studies in which ECG assessments were routinely conducted

Study ID	Placebo Control	Dose Tested	Total Treatment Days	Number of Subjects Treated with Duloxetine (M/F)	Age Range	Time of ECG in Relation to Dosing
Single Dose Study						
HMBA	Yes	60mg	1	6/10	21-53	Hour 0 & 6
HMBG	No	60mg	1	6/20	22-65	Hour 0 & 6
HMBJ	No	60mg	1	20/4	20-61	Hour 0 & 6
Multiple Dose Study (Fixed Dose)						
HMAS (O001)	Yes	60mg bid 80mg q d	7	12/0	18-40	Hour 0 & 6 Each Day
HMBD	Yes	60mg bid	4	8/8	18-55	Hour 0 & 6 Each Day
HMAZ	No	60mg bid	20	7/9	18-	Hour 6, 12 & 24 at Day 20
HMBN	No	60mg bid	19	6/6	18-	Hour 4, 6 & 8 at Day 19
Multiple Dose Study (Dose Escalation)						
HMAR	Yes	20mg bid 40mg bid 60mg bid 80mg bid	2 5 6 5	6/6	18-55	Hour 0 & 6 Each Day

HMAP	Yes	20mg bid	7	8/0	18-	Hour 3 Each Day
		30mg bid	7			
		40mg bid	7			
SBBN	Yes	60mg bid	7	3/9	18-65	Hour 4 at the first day of each dosing period
		80mg bid	7			
		100mg bid	7			
		120mg bid	7			
Total	--	20mg bid – 120mg bid	--	82/72	18-65	--

The intended treatment dose for SUI is 40 mg BID. In the above trials, 80 patients were treated with multiple doses of 60 mg BID, 24 patients were treated with multiple doses of 80 mg BID, and 12 were treated with multiple doses of 100 mg BID and 120 mg BID. As described in detail in Dr. Li's review, none of these phase I studies that measured ECGs identified a signal for QT prolongation.

Dr. Li's conclusions

Based on the clinical and non-clinical studies, Dr. Li concluded the following:

- No apparent QT safety signal has been identified from non-clinical studies at a dose equivalent to 60mg bid;
- No apparent QT safety signal has been identified from ten phase 1 and three phase 3 clinical studies;
- No evidence has suggested that syncope episodes observed in the clinical trials was related to ventricular arrhythmia (please see Section VII-C-10);
- No sudden death or Torsade de Pointes were observed in the clinical trials.

Despite the negative findings, Dr. Li made the recommendation that an additional clinical pharmacology study is necessary to characterize the effect of duloxetine on cardiac repolarization at the serum levels that would be expected with maximal inhibition of CYP1A2 and CYP2D6⁴. His recommendation is shared by Norman Stockbridge, a consultant from the Division of Cardioresenal Drug Products.

DRUDP requests in the approvable (AE) letter for duloxetine regarding the QTc interval

The following request comes from DRUDP's approvable letter for duloxetine dated

[

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⁴ Cmax and AUC of duloxetine increase about two-fold with inhibition of CYP2D6.

DNDP 2nd cycle review

Study SBBN

The clinical pharmacology study SBBN, a study that exposed patients to the highest doses of duloxetine so far in the development program (up to 120 mg BID for a week), was submitted to the IND since the first DNDP review cycle. Patients were treated with 40 mg BID of duloxetine for two weeks, followed by 60 mg BID, 80 mg BID, 100 mg BID, and 120 mg BID each for one week. ECGs were measured at screening, baseline, and then four hours after the first dose of each higher dose. Hence the on-drug ECGs essentially reflect the steady state of the previous dose; it does not reflect steady state on the higher dose. In the SBBN study report, the sponsor presented the mean and range of QTc (Fridericia [QTcF] and regression [QTcR] corrected⁵) for each of the dose groups. These mean values are summarized in the table below.

Mean QTc interval (Fridericia and Regression corrected) following Pre-dose and at Four Hours Post-dose for each Study Period

	Fridericia corrected		Regression corrected	
	Placebo N=3	Duloxetine N=12	Placebo N=3	Duloxetine N=12
Pre-dose	395.5	392.5	401.6	395.8
60 mg BID	398.3	391.1	403.7	396.4
80 mg BID	399.8	393.2	403.0	398.5
100 mg BID	396.7	391.2	401.8	396.8
120 mg BID	392.5	394.1	396.2	400.8

Source: Tables SBBN.12.11 and SBBN.12.12

Additional FDA Analyses

The sponsor did not present the mean change from baseline to endpoint for QTc by study period (for either correction method). In order to calculate the mean change from baseline to endpoint for each study period, I downloaded the ECG dataset provided by the sponsor. Using the QTc data included in the dataset, I could not reproduce the Mean QTc

⁵ The regression correction coefficient was 0.39.

tables included in the study report (and reproduced above). Additional analysis showed that the QTc included in the sponsor's dataset used the Bazett's correction. Because duloxetine causes a dose-related tachycardia, Bazett's is not an appropriate correction to use (it can cause an artifactual prolongation). Therefore, using the RR intervals and corresponding uncorrected QT intervals provided in the dataset, I calculated the QTcF and QTcR and the mean change from baseline to endpoint for each study period.

Mean QTc interval (Fridericia and Regression corrected) following Pre-dose and at Four Hours Post-dose for each Study Period

	Fridericia corrected			Regression corrected		
	Placebo N=3	Duloxetine N=12	Placebo corrected difference	Placebo N=3	Duloxetine N=12	Placebo corrected difference
60 mg BID	2.9	-1.5	-4.4	2.1	0.4	-1.7
80 mg BID	4.5	0.9	-3.6	1.5	2.6	1.1
100 mg BID	1.3	-1.4	-2.7	0.2	0.9	0.7
120 mg BID	-2.8	1.4	4.2	-5.3	4.7	10

Reviewer comment

Depending on the correction method used, the highest dose group of duloxetine in study SBBN is associated with a mean change from baseline to endpoint of 4.2-10 msec. Regardless of the correction method applied, there is no consistent trend in the mean change from baseline with increasing duloxetine dose. The placebo-corrected difference of 10 msec at the highest dose (regression method) derives from a mean change from baseline in the duloxetine group of 4.7 and that in the placebo group decreasing to -5. In a setting where there were a substantial number of placebo patients, and an adequate number (≥ 3) of baseline ECG measurements, I might put a little more faith in this estimate. However, the variability in the QT interval in general, and the specifics of there being only three patients in the placebo group and only one baseline ECG in each group suggests that the estimates of mean change from baseline in the placebo group are less than robust. Given that this study was not designed optimally to evaluate the effect of duloxetine on cardiac repolarization, it is difficult to interpret the placebo-corrected mean change from baseline.

To date, at doses intended for marketing and at doses close to 1.5X the intended dose, no signal for QTc prolongation has been identified. It should be noted that absence of identification of an effect is not equivalent to the absence of an effect, since the design of the clinical pharmacology studies with regard to assessment of the QTc has not been optimal. However, some reassurance can be taken from the fact that no effect on the QT interval has been observed in the clinical trials and clinical pharmacology trials, as drugs that have had an effect on the QTc have generally been detected in clinical trials (e.g., sertindole, ziprasidone).

Despite the absence of a finding, HFD-580 has asked for a study of the effect of full metabolic inhibition of duloxetine (CYP1A2 plus CYP2D6) on cardiac repolarization. ¹

1 DRUDP has made the assessment that a thorough assessment of the potential effect of duloxetine on cardiac repolarization must be conducted prior to consideration for marketing.

Since I have not reviewed the efficacy of duloxetine, I will not attempt to weigh the benefits of treatment of MDD with duloxetine against the potential risk of using a drug whose effect on cardiac repolarization has not been characterized with full metabolic inhibition (but which has no effect on QTc documented in the clinical trials). However, one could argue that with the indication of MDD, the calculus of weighing benefit and risk is different than with a purely symptomatic indication. Although it is important to fully characterize the effect of duloxetine on cardiac repolarization, this study could be done as an early Phase IV commitment.

/S/

Judith A. Racoosin, MD, MPH
Safety Team Leader, DNNDP

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Judith Racoosin
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