CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-427

Medical Review(s)

7/15/04

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

NDA: 21-427
Drug: duloxetine (Cymbalta)
Route: oral
Indication: major depressive disorder
Sponsor: Lilly
Materials reviewed: safety update, hepatic assessment section (dated 12/22/03); response to 3/15/04 data request (dated 4/1/04); response to 5/25/04 data request (dated 6/3/04); response to 6/10/04 data request (dated 6/11/04); response to 6/27/04 data request (dated 6/30/04); response to 7/1/04 data request (dated 7/7/04); response to 7/12/04 data request (dated 7/13/04)

1 Introduction

Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, is indicated for the treatment of major depressive disorder (MDD). In addition to the MDD indication here in the Division of Neuropharmacological Drug Products (DNDP), this drug product is concurrently being evaluated for the indications of stress urinary incontinence (SUI) in the Division of Reproductive and Urologic Drug Products (DRUDP) and painful diabetic neuropathy (PDN) in the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP).

During the first cycle review of duloxetine for stress urinary incontinence (SUI) by DRUDP, the safety issue of hepatotoxicity became prominent. In my memo dated 9/22/03, I reviewed the data on hepatotoxicity with duloxetine that had been submitted with the response to the approvable letter. I concluded that 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). 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 were unconfounded, however. Finally, some cases suggested that combined use of duloxetine and ethanol may potentiate the hepatotoxicity associated with these agents.

Regarding the potential for duloxetine-related hepatotoxicity, we made the following statements and requests in the second duloxetine approvable letter:

- We have added language to the PRECAUTIONS section of the labeling that describes the observed transaminase abnormalities and cases of severe liver injury associated with the combination of duloxetine use and ethanol abuse.

• We request that you provide any additional available information on the severe liver injury cases that occurred in two placebo patients.
• We request that you commit to close monitoring of postmarketing AEs for duloxetine with regard to hepatotoxic adverse events, as follows:

a. Expedited reporting of all liver-related AEs received during the postmarketing period.
b. Quarterly summaries on all liver related AEs along with estimates of drug usage for that specific quarter and an explanation of the method used to estimate drug usage.
c. Detailed follow-up information on reported cases of hepatotoxicity.

Language included in the proposed labeling pertaining to liver function follows below:

Clinical Pharmacology, Special Populations subsection:

Hepatic Insufficiency — Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and elimination. After a single 20 mg dose of duloxetine, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although Cmax was similar to normals in the cirrhotic patients, the half-life was about 3 times longer (*see* PRECAUTIONS). It is recommended that duloxetine not be administered to patients with : C J hepatic insufficiency (*see* DOSAGE AND ADMINISTRATION).

Precautions, General subsection:

[ ]

Precautions, Use in Patients with Concomitant Illness

DOSAGE AND ADMINISTRATION).

Precautions, Information for Patients

[ ]

Precautions, Drug Interactions

Duloxetine May Have a Clinically Important Interaction with the Following Other Drugs:
Alcohol — When duloxetine and ethanol were administered several hours apart so that peak concentrations of each would coincide, duloxetine did not increase the impairment of mental and motor skills caused by

alcohol. [ ]

[ ]

Dosage and Administration, Special Populations

Dosage for [ ] Impaired Patients — [ ]

The current submission is Lilly's response to the second approvable letter. Although we only requested follow-up on the two placebo patients with severe liver injury in the last approvable letter, the sponsor submitted a full summary of the liver-related laboratory data and the reports of eight hepatobiliary expert consultants. This memo will review the laboratory analyses as well as discuss the findings/conclusions of the sponsor's expert liver consultants.

After reviewing the sponsor's initial submission, I requested additional data analyses, and narratives for patients who had liver-related SAEs or discontinued due to a liver-related AE (see Appendix 1). The response to the data request was submitted on 4/1/04. Review of that submission led to the request of additional clarification of patients who discontinued due to liver related AEs because the list included in the sponsor's 4/1/04 submission was not inclusive of all patients who discontinued due to liver related AEs (see Appendix 2).

2 Methods

Section 5 of the safety update entitled "Hepatic Assessment" included analyses of two databases:

All Placebo-Controlled Studies Safety Database: Includes hepatic laboratory data from all locked placebo-controlled studies, regardless of indication, as of 01 October 2003

- Studies[1] HMAG, HMAH, HMAI, HMAQa, HMAQb, HMATa, HMATb, HMAVa, HMAW, HMAYa, HMAYb, HMBHa, HMBHb, HMBO, HMCB, SAAA, SAAB, SAAH, SAAI, SAAL, SAAW, SBAB, SBAF, SBAM, SBAT, SBAV, SBAX, SBBA.

Overall Duloxetine Exposures Database: Includes hepatic laboratory data from all patients who received duloxetine during a Lilly study, regardless of indication, as of 01 October 2003

- Studies E001, HMAG, HMAH, HMAI, HMAQa, HMAQb, HMATa, HMATb, HMAU, HMAVa, HMAW, HMAYa, HMAYb, HMBC, HMBHa, HMBHb,

[1] Studies listed in red are in the MDD development program, those in blue are in the pain development program, and those in green are in the SUI development program.

HMBO, HMBT, HMBY, HMCB, SAAA, SAAB, SAAH, SAAI, SAAL, SAAW, SBAB, SBAF, SBAM, SBAT, SBAU, SBAV, SBAW, SBAX, SBAY, SBBA, SBBM.

The [redacted] databases, derived from the Japanese studies were not included in the above databases; however, individual cases of hepatotoxicity from these databases were included in the submission.

Hepatic laboratory analytes included ALT, AST, GGT, total bilirubin (TBILI), and alkaline phosphatase (ALKPH). [redacted] reference ranges were used. The sponsor included tables summarizing change from baseline to endpoint value and from baseline to maximum value for each of the analytes (these analyses generally included all patients and not just those who had normal baseline values). Tables summarizing emergence of abnormally high ALT values were stratified for baseline ALT (normal vs. elevated). Shift tables were also provided.

Patients meeting the criteria for a modified "Hy's rule" (ALT $\geq$3X and TBILI $\geq$1.5X upper limit of normal [ULN]) were identified; the sponsor included narratives describing those patients that met the criteria.

In the sponsor's April 1, 2004 response to my questions of March 15, 2004 (see Appendix 1), they noted that in the database used to generate the hepatic laboratory tables for the "Complete Response to the Approvable Letter (Second Cycle)" dated December 22, 2003, for one study (SBAX for stress urinary incontinence) the first post-baseline visit had been inadvertently incorporated as the baseline value for that study in the integrated database. The April 1, 2004 submission includes replacement tables for all of the tables submitted as part of the liver update in the December 22, 2003 response, in addition to the responses to my specific questions. The tables included in this review will be those that have been corrected. The updated tables show that the N for the placebo group has increased by four, and the N for the duloxetine group has increased by about 34.

In my 3/15/04 data request, I asked Lilly to repeat the mean change from baseline to endpoint, mean change from baseline to maximum value, and outlier analyses on a subset of studies that included only those that used a fixed dose design so that a dose response relationship could be evaluated. Lilly used the following criteria to select fixed dose design studies:

- Patients received a single dose throughout the study
- A forced titration was employed and was completed within 1 week after randomization
- For studies that started with targeted doses and allowed de-escalation for a short time, the patient must have been escalated back to the targeted dose level within a defined time period in order to continue in the study

Seventeen of the 28 studies in the all placebo-controlled studies safety database fulfilled one of these criteria. The results shown below for this subset are referred to as the "fixed dose" subset.

In my data request dated 5/25/04 (questions generated by my review of the 4/1/04 submission, see appendix 2), I requested the list of preferred terms that were used to search for the liver-related SAEs and AEs leading to discontinuation. The list follows below (Table 2, 6/3/04 response).

MedDra Preferred Terms Used to Search for Liver-Related SAEs and AEs Leading to Discontinuation

MedDra Preferred Term
Hepatic enzyme increased
Hepatic function abnormal
Hepatic function abnormal NOS
Liver function test abnormal
Alanine aminotransferase increased
Aspartate aminotransferase increased
Gamma-glutamyltransferase increased
Hyperbilirubinaemia
Jaundice
Jaundice NOS
Transaminases increased

After reviewing this list of MedDRA Preferred Terms used in the search, I was concerned that more severe liver-related events might have been missed due to the absence of terms that would identify such events (e.g., hepatitis, liver failure, liver necrosis, etc.). As a result, on June 10, 2004, I sent an additional request for a search of the safety database using a much broader search methodology that would capture the full range of severity of liver-related events. See Appendix 3 for the list of specific requests.

3 Update on patients meeting Hy's law thresholds for ALT and total bilirubin discussed in 9/22/03 memo

3.1 Placebo group

In response to DNDP's request in the second approvable letter, Lilly provided additional details about the placebo-treated patients who had LFTs that met the Hy's law criteria. These cases are summarized below.

3.1.1 Subject HMBC 606-6602

This 41 yo Caucasian male, with no known history of hepatitis, cholecystitis, Wilson's disease, or biliary obstruction, participating in a MDD study had normal transaminases and a slightly elevated TBILI of 1.4 at baseline. Fractionation of the baseline TBILI showed an unconjugated hyperbilirubinemia (direct bilirubin was 0.3 mg/dl), consistent with Gilbert's syndrome. The patient took duloxetine 60 mg/day for 12 weeks in an open phase of the trial. Fifteen weeks into the placebo period, the TBILI increased to 2.2 mg/dl, and the ALT increased to 405 (nl 6-43; see table below). Viral serologies were negative. Concomitant medications were vitamin C and Actifed. The patient discontinued duloxetine two days after the abnormal LFTs were detected. About one month later, they had returned to normal (including the TBILI).

Table 5.22. Patient F1J-MC-HMBC 606-6602 Hepatic Laboratory Values

Date	Visit	AST 11-36 U/L	ALT 6-43 U/L	ALKPH 31-129 U/L	GGT 10-61 U/L	TBILI 0.2-1.2 mg/dL
	1	27	35	55	37	1.4
	5	18	27	63	35	1.2
	8	**45**	**62**	56	**94**	0.8
	14	**164**	**405**	99	**380**	2.2
	15	26	35	57	44	0.9

Reviewer's comment: Given the development of these LFT abnormalities 15 weeks into the placebo period, it is unlikely that they can be attributed to the 12 weeks of duloxetine treatment in the open label period of the relapse prevention study. Unfortunately, other than viral serologies, no work-up was done to discover the etiology of the patient's LFT abnormalities.

3.1.2 Subject HMBH 120-3017

This 83 yo Caucasian male with no reported history of alcoholic liver disease, Wilson's disease, cholecystitis, or biliary obstruction was treated with placebo in a MDD study. His baseline labs were within normal limits (see table below). 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 reportedly taken throughout the trial were naproxen, ranitidine, glucosamine, aspirin, vitamins, calcium, and Metamucil. He discontinued duloxetine on the day the elevated LFTs were detected. One month later his LFTs had normalized, with the exception of the GGT which had declined substantially.

Table 5.23. Patient F1J-MC-HMBH 120-3017 Hepatic Laboratory Values

Date	Visit	ALT 6-35U/L	AST 11-36 U/L	ALKPH 35-187 U/L	GGT 10-50 U/L	TBILI 0.2-1.2 mg/dL
	1	14	21	48	43	0.5
	6	12	18	57	48	0.5
	7	**130**	**87**	117	**337**	**2.5**
	999	12	19	57	**87**	0.6

Reviewer's comment: The elevated GGT along with the elevated TBILI somewhat out of proportion with the less markedly elevated transaminases suggests an obstructive process that resolved spontaneously. However, it would have been helpful for the patient to have been worked up to reveal the source of his LFT abnormalities.

3.2 Duloxetine group

In the "Hepatic Assessment" section of the safety update, Lilly summarized the details of the duloxetine-treated patients whose LFTs had met the Hy's law criteria. These cases had been previously described in documents submitted prior to the second approvable action. In this submission, they provided new information only for patient HMBT 305-3512. The narrative summaries included in this section are adapted from my memo dated 9/22/03, unless otherwise indicated as an "update".

3.2.1 HMBT 305-3512

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 painful diabetic neuropathy. 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.

Date	ALT	AST	AP	GGT	Total Bilirubin
(baseline)	27	27	71	51	0.4
	19	13	55	25	0.4
	441	136	128	588	1.9
4/21/03	Duloxetine discontinued (pt reportedly took no dose that day)				
	90	34	84	266	0.5
	50	32	70	154	0.7
	30	30	67	98	0.5
	23	18	65	27	0.4

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 repurcussions

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 ethanol use, but history of ethanol use was not described in the case report. Dr. Senior's final assessment was that it was "probable duloxetine-induced transient mild hepatotoxicity, possibly caused by a combined effect with some other drug, such as alcohol, acetaminophen, or other."

Reviewer comment: The rapid decrease in ALT and TB observed one day after discontinuing duloxetine, despite the patient apparently staying on the drug for at least four days after the abnormal labs were drawn is a perplexing finding that Dr. Senior did not address in his review. If the "bump" in ALT, GGT, and TB were related to duloxetine, it would be unexpected that these values would fall so rapidly within one day of drug discontinuation. At the same time, there is an absence of evidence with regard to other potentially explanatory mechanism such as the ingestion of potential hepatotoxins (e.g., ethanol or acetaminophen).

Sponsor update: 150 days after the patients last duloxetine dose she was hospitalized with jaundice, nausea, and vomiting. At surgery she was found to have a common bile duct stone.

3.2.2 HMAW 500-5254

Subject 500-5254 (HMAW): This was a 43 yo male with history of diabetes and ethanol abuse who was treated with duloxetine for painful diabetic neuropathy. 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 ([ ] after about 6.5 months on duloxetine). The patient was hospitalized on [ ] 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)**

Lab Parameter (nl range)	ALT (6-43)	AST (11-36)	AP (31-129)	GGT (10-61)	Total Bilirubin (0.2-1.2)
(baseline)	31	33	87	68	0.9
	20	27	131	114	0.9

(last value on 60 q d)					
(on 60 BID for 2 mos)	28	26	149	92	1.1
(on 60 BID for 3 mos)	37	44	115	159	0.4
Stopped study drug 8/9/04					
	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 feto-protein. The abdominal US showed ascites, a CT showed hepatosplenomegaly and fatty liver, and laboratory tests showed prolonged INR (1.25 on[redacted]), reduced serum albumin, target cell anemia, and thrombocytopenia (all signs of decompensated liver disease). Note: the accompanying laboratory data sheet showed low platelets on[redacted] (124K down from 240K in[redacted]), but no albumin value was reported for the period corresponding to the episode of serious hepatic injury (it was normal in[redacted]. 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, Dr.[redacted] 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. Dr.[redacted] 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 ([redacted]). Notably, in[redacted] 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 slightly elevated prior to the acute decompensation, and then rose markedly along with the transaminases, such that the case is not consistent with the definition of Hy's law (e.g., that the liver injury observed occurs without evidence of obstruction). Finally, the

GGT began to rise again several months after duloxetine discontinuation, suggesting some ongoing hepatobiliary process.

3.2.3 321G A06706 [illegible] database)

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 [illegible] the physician decreased the daily dose to 20 mg/day. One month later in early [illegible] 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)**

Lab Parameter (nl range)	ALT (7-45)	AST (10-35)	AP (80-240)	GGT (6-60)	Total Bilirubin (0.2-1.2 mg/dl)
(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
(30 q d for 4 mos)	53	91	308	123	1.4
(10 q d for 2 weeks)	528	816	400	401	2.9
(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 improved 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 does not qualify as a "Hy's law" case.

3.2.4 321G A09505 ([ ] database)

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
ς - --	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.

4 Hepatic Assessment Results

4.1 Laboratory Analyses

4.1.1 Mean change from baseline

The following table summarizes the mean change from baseline to end of study and mean change from baseline to maximum for the duloxetine (all doses) and placebo groups in the all placebo-controlled studies safety database. (Updated table 5.1 and 5.2, pp. 10-13, 4/1/04 submission)

FDA Table 1. Mean change from baseline to endpoint and maximum value by treatment group and laboratory parameter, all placebo controlled studies database

	Duloxetine (all doses)		Placebo	
	End	Maximum	End	Maximum
ALT (U/L)	1.8	5.0	-0.7	2.1
	(n=4201)		(n=2871)	
AST (U/L)	1.2	3.4	-0.3	1.8
	(n=4184)		(n=2858)	
TBILI (μmol/L)	-0.09	1.0	0.02	1.1
	(n=4199)		(n=2875)	
ALKPH (U/L)	1.9	4.9	-0.1	2.9
	(n=4212)		(n=2879)	
GGT (U/L)	-0.7	1.6	-0.5	2.2
	(n=4013)		(n=2667)	

As can be seen above, the mean change from baseline to endpoint and from baseline to maximum value was slightly higher in the duloxetine group than placebo for ALT, AST, and ALKPH.

4.1.2 Mean change from baseline by dose (fixed dose subset)[2]

Table 3 (p. 61-2, 4/1/04 submission) shows the mean change from baseline to endpoint by dose and laboratory parameter. There was little suggestion of a dose-response relationship for any of the LFTs (ALT, AST, GGT, ALKPH, TBILI). Table 4 (p. 64-5,

[2] The mean change from baseline analyses in the fixed dose subset included only patients who had normal baseline LFTs.

4/1/04 submission) shows the mean change from baseline to maximum value by dose and laboratory parameter. There was a suggestion of a dose-response relationship for ALKPH only (placebo [3.0], <40 [2.6], 40 [4.6], 60 [4.7], 80 [5.5], ≥120 [7.2]).

4.1.3 Liver function test outliers

The results shown in the following tables include only patients who had normal laboratory parameters at baseline.

4.1.3.1 All placebo-controlled studies group

The table below shows the frequency of outliers at various thresholds for each treatment group and laboratory parameter (derived from sponsor updated tables 5.3 and 5.5, pp. 14-15, 4/1/04 submission and table 1a, pp. 9-11, 6/3/04 submission).

FDA Table 2. Percentages of outliers by treatment group and laboratory parameter, all placebo controlled studies database, patients with normal baseline values.

	Duloxetine (all doses)				Placebo			
	Any (%)	3x (%)	5x (%)	10x (%)	Any (%)	3x (%)	5x (%)	10x (%)
ALT (U/L)	5.8	1.05	0.51	0.16	3.8	0.23	0.04	0
	(n=3732)				(n=2568)			
AST (U/L)	4.3	0.4	0.2	0.05	2.4	0.04	0	0
	(n=3936)				(n=2693)			
ALKPH (U/L)	1.5	0	0	0	0.9	0	0	0
	(n=4046)				(n=2797)			
GGT (U/L)	2.2	0.14	0	0	1.8	0.24	0.08	0
	(n=3662)				(n=2469)			

	Duloxetine (all doses)				Placebo			
	Any (%)	1.5x (%)	3x (%)	≥ 2 mg/dl (%)	Any (%)	1.5x (%)	3x (%)	≥ 2 mg/dl (%)
TBILI (μmol/L)	0.6	0.1	0.05	0.07	0.7	0.04	0	0.04
	(n=4153)				(n=2852)			

4.1.3.2 Fixed dose subset

As can be seen in the tables below[3], in the subset of fixed dose studies, there was a dose response relationship observed for ALT and AST outliers at the 3x ULN and 5x ULN (and at 10x ULN for ALT) thresholds (derived from Table 5, p. 67, 4/1/04 submission and table 1b, pp. 13-16, 6/3/04 submission). There was no evidence of a dose response relationship for TBILI, ALKPH, or GGT.

[3] There is no table included in this section for ALKPH because no patient with a normal baseline value had an on-treatment value exceeding 3X ULN.

FDA Table 3. Percentages of ALT outliers by treatment group, all placebo controlled studies database, fixed dose subset, patients with normal baseline values.

Treatment Group	3xULN (%)	5xULN (%)	10xULN (%)
Placebo (N=1783)	0.2	0.06	0
DLX<40 (N=534)	0.2	0	0
DLX=40 (N=145)	0.7	0	0
DLX=60 (N=467)	0.6	0.2	0.2
DLX=80 (N=1094)	1.2	0.5	0.2
DLX≥120 (N=365)	2.2	1.1	0.3

FDA Table 4. Percentages of AST outliers by treatment group, all placebo controlled studies database, fixed dose subset, patients with normal baseline values.

Treatment Group	3xULN (%)	5xULN (%)	10xULN (%)
Placebo (N=1783)	0.05	0	0
DLX<40 (N=534)	0	0	0
DLX=40 (N=145)	0	0	0
DLX=60 (N=467)	0.6	0.2	0
DLX=80 (N=1094)	0.3	0.2	0.1
DLX≥120 (N=365)	0.8	0.3	0

FDA Table 5. Percentages of GGT outliers by treatment group, all placebo controlled studies database, fixed dose subset, patients with normal baseline values.

Treatment Group	3xULN (%)	5xULN (%)	10xULN (%)
Placebo (N=1783)	0.3	0.1	0
DLX<40 (N=534)	0	0	0
DLX=40 (N=145)	0	0	0
DLX=60 (N=467)	0.2	0	0

DLX=80 (N=1094)	0	0	0
DLX≥120 (N=365)	0.6	0	0

FDA Table 6. Percentages of TBILI outliers by treatment group, all placebo controlled studies database, fixed dose subset, patients with normal baseline values.

Treatment Group	1.5xULN (%)	3xULN (%)	≥ 2 mg/dl (%)
Placebo (N=1783)	0.05	0	0.05
DLX<40 (N=534)	0.5	0.4	0.4
DLX=40 (N=145)	0	0	0
DLX=60 (N=467)	0.2	0	0.2
DLX=80 (N=1094)	0	0	0
DLX≥120 (N=365)	0	0	0

4.2 Discontinuations due to liver abnormalities

In the process of reviewing the response to the second approvable letter, it became apparent that discontinuations due to liver abnormalities had been coded in a variety of ways. In some cases, patients who had LFT abnormalities were identified by investigators as having had an adverse event. In some cases LFT abnormalities led to patients being discontinued for "significant laboratory abnormalities", and in some cases, sponsor or investigator decisions to discontinue a patient were driven by the occurrence of LFT abnormalities. These distinctions should be kept in mind as this section is read. In section 4.4.3 below, I present the summary tables that include patients who discontinued for liver-related problems, regardless of how they were identified or coded.

4.2.1 Discontinuations due to liver-related AEs

In the placebo-controlled studies database, no placebo patients and 0.1% (4/4507) of duloxetine patients discontinued for liver related AEs (preferred terms "liver function test abnormal" and "alanine aminotransferase increased"). In the fixed dose subset, two duloxetine-treated patients discontinued due to the AE "liver function test abnormal"; one was in the 80 mg group and one was in the ≥120 mg group.

In the overall duloxetine exposures database, 0.2% (20/8454) of duloxetine patients discontinued due to liver related AEs. Lilly's original search of the safety database for liver-related AEs identified 19 cases. However, when the search was broadened (at DNDP's request) to include terms reflecting the full range of severity among liver events (using the MedDRA Higher Level Group Terms "Hepatic and Hepatobiliary Disorders" and "Hepatobiliary Investigations"), one additional case was identified. This was patient HMBT 302-3202 who had an AE coded to the preferred term "hepatitis" (see section 4.4.2.3).

The preferred terms for which patients discontinued are listed in the sponsor's table below (Updated Table 10, p. 15, 6/11/04 submission).

Liver-Related Adverse Events Reported as Reason for Discontinuation
MedDra Preferred Terms
All Patients Who Received Duloxetine
Overall Duloxetine Exposures Safety Database

Event	DULOX (N=8454) n(%)
OVERALL	20(0.2%)
Liver function test abnormal	9(0.1%)
Alanine aminotransferase increased	4(0.0%)
Aspartate aminotransferase increased	2(0.0%)
Gamma-glutamyltransferase increased	1(0.0%)
Hepatitis NOS	1(0.0%)
Hyperbilirubinaemia	1(0.0%)
Jaundice NOS	1(0.0%)
Transaminases increased	1(0.0%)

4.2.1.1 Specific AEs leading to discontinuation

4.2.1.1.1 HMAY 150-6005

This 26 year old Caucasian female was taking duloxetine 40 mg BID for MDD. During open label therapy 142 days into the study she was noted to have an ALT of 115 and an AST of 66; her ALT had been slowly rising for two months from normal baseline values. TBILI was 0.8 concurrent with the abnormal transaminases. She stopped the drug three days later. About five weeks after duloxetine was discontinued, the TBILI increased to 1.5 mg/dl, but the transaminases had fallen to 22 and 25 by then (ALT and AST, respectively).

4.2.1.1.2 HMBY 110-1901

This 50 year old Caucasian female was taking duloxetine in a dose escalation study for safety in patients being treated for MDD. She was treated with up to 120 mg per day for six weeks, and then decreased to 90 mg per day in the extension study. About one week in to the extension study, the patient had elevated ALT and AST, but total bilirubin was

normal. She was discontinued from duloxetine the next day and her LFTs normalized within about three weeks. See the table below for lab values.

HMBY 110-1901

Date	Visit	AST (9-62U/L)	ALT (5-80 U/L)	CPK	ALK Phos (31-168 U/L)	GGT (5-127 U/L)	T. Bili (0.2-1.3 mg/dL)
	1	18	16	58	66	13	0.9
	8	201	408	59	91	28	1.0
	8A	64	177	44	82	27	0.6
	9	52	106	49	74	25	0.7
	9A	35	55	54	73	23	0.7

4.2.1.1.3 SBBA 118-2801

This 63 year old female of African descent was taking duloxetine 80 mg daily for SUI. After having normal baseline LFTs, she manifested abnormal transaminases (but normal TBILI) on laboratory tests drawn on day 85 of the study. She discontinued duloxetine two days later. Her LFTs improved but did not completely normalize by three weeks after the last dose. See the table below for lab values.

SBBA 118-2801

Date	Visit	ALT (6-34 U/L)	AST (9-35 U/L)	AlkPhos (31-106 U/L)	GGT (4-49 U/L)	T. Bilirubin (0.2-1.2 mg/dl)
	1	26 U/L	33 U/L	67 U/L	N/A	0.3 mg/dl
	3	183 U/L	122 U/L	89 U/L	N/A	0.5 mg/dl
	3	194 U/L	122 U/L	89 U/L	232 U/L	0.5 mg/dl
	3	116 U/L	73 U/L	85 U/L	198 U/L	0.4 mg/dl
	3	64 U/L	54 U/L	66 U/L	141 U/L	0.6 mg/dl
/2	4	65 U/L	53 U/L	67 U/L	N/A	0.6 mg/dl

4.2.1.1.4 SBAV 120-3009

This 69 year old Caucasian female was taking duloxetine 80 mg daily for SUI. After having normal baseline LFTs, she manifested abnormal LFTs on laboratory tests drawn on day 43 of the study with an ALT of 354 and an AST of 185. Concurrent TBILI was 0.7 mg/dl. Two weeks later the ALT was 57 and the AST was 33. She discontinued duloxetine about one week because of "elevated LFTs".

4.2.1.1.5 SBAW 100-6000 (SBAV/SBAW 100-1002)

This 64 year old Caucasian female was taking duloxetine 80 mg daily for SUI. After having normal baseline LFTs, she manifested abnormal LFTs on laboratory tests drawn on day 256 by an insurance company. The actual lab values were not reported in the narrative. Her primary care physician advised her to discontinue the duloxetine. The results of the dechallenge were not reported.

In response to a request for the insurance company lab values, the sponsor provided the following information:

ALT = 54 U/L (insurance company normal range 0 – 45 U/L)
AST = 63 U/L (insurance company normal range 0 – 33 U/L)
ALKPH = 171 U/L (insurance company normal range 30 – 125 U/L)
GGT = 103 U/L (insurance company normal range 0 – 45 U/L)

TBILI = 0.5 mg/dl (insurance company normal range 0.2 – 1.2 mg/dl)
Hepatic B surface antigen = negative
Hepatitis C antibody = negative

Reviewer comment: The LFT abnormalities identified by the insurance company are modest, and suggest obstruction more than hepatocellular injury.

4.2.1.1.6 SBAW 114-6708 (SBAV/SBAW 114-2412)

This 53 year old Hispanic female was taking duloxetine 80 mg daily for SUI. After having normal baseline LFTs, she manifested abnormal LFTs on laboratory tests drawn on day 40 of the study with an ALT of 310 and an AST of 155. The ALT peaked at 361 one week later. Concurrent TBILI was 0.3 mg/dl. She discontinued duloxetine about one week later; three weeks later the transaminases had diminished, and subsequently normalized two visits later.

4.2.1.1.7 SBAY 126-3601

This 49 year old Caucasian female was taking duloxetine 80 mg daily for SUI. After having normal baseline LFTs, she manifested abnormal LFTs on laboratory tests drawn on day 83 of the study with an ALT of 140 and an AST of 73. The ALT peaked at 291 nine days later. She discontinued duloxetine about five days later. The sponsor reported that the adverse event resolved ten days after discontinuation, but did not provide LFT values corresponding to that date. However, lab values for two months after discontinuation showed the transaminases were still elevated in the same range, and the ALT continued to increase subsequent to that blood draw.

Date	Visit	ALT (6-34 U/L)	AST (9-35 U/L)	AlkPhos (31-106 U/L)	GGT (4-49 U/L)	T. Bilirubin (0.2-1.2 mg/dl)
	1	30 U/L	28 U/L	59 U/L	29 U/L	0.4 mg/dl
	2	27 U/L	24 U/L	50 U/L	19 U/L	0.5 mg/dl
	3	140 U/L	73 U/L	57 U/L	42 U/L	0.4 mg/dl
	3A	291 U/L	150 U/L	61 U/L	76 U/L	0.4 mg/dl
Last dose of study drug 26 Jun 2001						
	3M	79 U/L	39 U/L	50 U/L	35 U/L	0.5 mg/dl
	4	262 U/L	115 U/L	61 U/L	56 U/L	0.3 mg/dl
	4A	234 U/L	119 U/L	55 U/L	43 U/L	0.3 mg/dl
	501	274 U/L	118 U/L	57 U/L	59 U/L	0.4 mg/dl
	999b	600 U/L	281 U/L	81 U/L	92 U/L	0.8 mg/dl
	999c	68 U/L	31 U/L	58 U/L	41 U/L	0.5 mg/dl
	999d	67 U/L	32 U/L	62 U/L	42 U/L	0.4 mg/dl

In response to a request to provide more information on this patient, the sponsor obtained this follow-up: The patient had a liver biopsy about two weeks after the ALT was measured at 600. The diagnosis attached to the biopsy was "mild chronic lobular hepatitis". A few weeks after the biopsy, the ALT had fallen to 68. TBILI values drawn concurrently with the abnormal ALTs did not show any abnormalities.

4.2.1.1.8 SBAY 131-4107

This 40 year old Caucasian female was taking duloxetine 80 mg daily for SUI. After having normal baseline and visit 1 LFTs, she visited her primary care doctor who found her to have an AST of 122 on day 12 of duloxetine treatment (no ALT or TBILI were

reported). She requested to discontinue from the trial based on the elevated AST. Her termination visit LFTs were reportedly within normal limits, but it was unclear from the narrative how many days passed between her last duloxetine dose and the termination visit blood draw.

4.2.1.1.9 SAAW 029-1427

This 54 year old Caucasian female was taking duloxetine 20 mg daily for SUI. After having normal baseline LFTs, she manifested abnormal LFTs on laboratory tests drawn on day 54 of the study with an ALT of 277, an AST of 91, and a GGT 297. Concurrent TBILI was 0.8 mg/dl. Three days later she discontinued duloxetine. Three days after that the transaminases were declining back to the normal range (ALT 72, AST 25).

4.2.1.1.10 E001 802-8208

This 57 year old Caucasian female was taking duloxetine 20 mg daily for MDD. After having normal baseline LFTs, she manifested abnormal LFTs on laboratory tests drawn about two weeks into the study with an ALT of 109 and a GGT of 320. Concurrent TBILI was 0.5 mg/dl. Two days later she discontinued duloxetine. LFTs drawn about one month later were within normal limits.

4.2.1.1.11 HMAV 028-2808

This 48 year old Caucasian male was taking duloxetine 60 mg BID. After having normal baseline LFTs, he manifested abnormal LFTs on laboratory tests drawn on day 56 of the study with an ALT of 581, an AST of 199, and a GGT 297. There was no concomitant TBILI abnormality. Two days later he discontinued duloxetine. One week later the transaminases were declining (ALT 325, AST 95), but did not return back towards the normal range for about one month (ALT 70, AST 63).

Reviewer note: *The narrative indicated that the patient had begun to increase his alcohol intake shortly before the "bump" in the transaminases. Of note is that the ALT was elevated substantially more than the AST, which is the reverse of what is generally seen with alcoholic hepatitis.*

4.2.1.1.12 HMAU 103-1309

This 43 year old Argentine female was taking duloxetine 60 mg BID (after two weeks of 40 mg BID) for MDD. She had slightly abnormal LFTs at baseline (82 with an ULN of 80). About six months into the study she manifested abnormal LFTs with an ALT of 123; it remained elevated for the next several months despite decreasing the dose to 40 mg BID, and peaked about four months later at 373. There was reportedly no associated abnormality of TBILI (values not submitted). About a month before the peak ALT, viral serologies revealed a positive Hepatitis B Core antibody and a positive Hepatitis C antibody. Duloxetine was discontinued about one week after the peak ALT. ALT had fallen to 126 about two months after the last duloxetine dose.

4.2.1.1.13 HMAU 106-1605

This 60 year old Argentine female was taking duloxetine 40 mg BID for MDD. After having normal baseline LFTs, she manifested abnormal LFTs on laboratory tests drawn

on study day 54 with an ALT of 445 and an AST of 155. Reportedly there was no associated TBILI abnormality. Viral serologies were negative. Five days later she discontinued duloxetine. LFTs drawn about three weeks later showed declining values (ALT 136, AST 57).

4.2.1.1.14 HMAU 107-1722

This 56 year old Argentine female was taking duloxetine 60 mg BID for MDD. After having normal baseline LFTs, she manifested abnormal LFTs on laboratory tests drawn on study day 61 with an ALT of 345 and an AST of 158. Nine days later the LFTs had declined slightly. About two weeks later, after the patient initiated a dose reduction due to dyspepsia and nausea, her dose was lowered to 40 mg BID. Over the next three weeks her LFTs normalized.

Four months later she complained of nausea and vomiting and was found to have an ALT of 393 and an AST of 311. She discontinued duloxetine ten days later. Although she reported a change in urine and feces color as well as right upper quadrant pain, the narrative reports that there was no associated TBILI abnormality (actual values were in the range of 0.2-0.4 mg/dl). LFTs drawn over the next several weeks slowly normalized. The patient was also seen during her acute symptomatic period by a hepatic consultant. Viral serologies were negative and a sonogram showed hepatic duct dilatation but no gallstones. The consultant considered her transaminitis to be related to duloxetine.

4.2.1.1.15 HMAU 131-5139

This 36 year old Hispanic female was taking duloxetine 60 mg bid for depression. About nine months into treatment with duloxetine, her AST was measured at 123 (it was normal at baseline); at the same time her CPK was measured at 3256 (nl 20-453) and CK-MB was 12.9 (nl 0-4.9 ng/ml). Based on these lab values, the site instructed the patient to stop taking the duloxetine. Her last dose was three weeks after the labs were drawn. A follow-up AST returned to normal ten days later, but no additional CPK values were reported.

4.2.1.1.16 HMAU 142-6308

This 43 year old Hispanic female was taking duloxetine 40 mg bid for depression. Her total bilirubin was normal at baseline. Four days into treatment her dose was decreased to 20 mg bid for complaints of dyspnea and paresthesias. After one week of treatment, her TBILI was slightly elevated (nl range >21; see table below). Over the next several months the TBILI slowly increased. The patient was evaluated and diagnosed with Gilbert's syndrome.

T.BILI	(H)	25.65	umol/L	2	21
T.BILI	(H)	22.23	umol/L	2	21
T.BILI	(H)	23.94	umol/L	2	21
T.BILI	(H)	32.49	umol/L	2	21
T.BILI	(H)	23.94	umol/L	2	21
T.BILI	(H)	25.65	umol/L	2	21
T.BILI	(H)	32.49	umol/L	2	21

Duloxetine was discontinued on February 20, 2001 because of elevated bilirubin.

T.BILI	(H)	30.78	umol/L	2	21	
T.BILI	(H)	30.78	umol/L	2	21	
T.BILI	(H)	32.49	umol/L	2	21	
I.BILI	(H)	25.65	umol/L	0	21	
I.BILI	(H)	27.36	umol/L	0	21	

Concurrent with the hyperbilirubinemia, the AST and ALT increased slightly, but did not go above the high end of normal (however, the actual values were not provided). By April 17, 2001, the TBILI normalized.

4.2.1.1.17 HMBT 502-5209

This 45 year old Caucasian female was taking duloxetine 60 mg bid for painful diabetic neuropathy. After having normal baseline LFTs, she manifested abnormal LFTs on laboratory tests drawn on day 49 of the study with an ALT of 334, an AST of 145, and TBILI 1.4 mg/dl. Two days later she discontinued duloxetine. About one week later the transaminases were declining back to the normal range (ALT 181, AST 72, TBILI 1.3). About one month after the last dose, the LFTs normalized.

4.2.1.1.18 HMBT 305-3512

See description above in section 3.2.1

4.2.1.1.19 HMBT 302-3203

See description below in section 4.4.2.3

4.2.1.1.20 HMAW 500-5254

See description above in section 3.2.2

4.2.2 Patients who discontinued due to LFT abnormalities who were not identified through the sponsor's original search

During her review of clinical study reports that accompanied the 12/22/03 submission, Dr. Roberta Glass identified several hepatic-related AEs resulting in discontinuation. When I matched these cases up with those that the sponsor had submitted, I noted that several had not been identified by the sponsor's search. In response to our request for clarification on why these patients had not been captured by the sponsor's search strategy, the sponsor provided the following explanations.

4.2.2.1 Patients who discontinued due to "other significant lab values"

Lilly reports that in fibromyalgia and diabetic neuropathic pain studies the reason "other significant lab values" was used to identify patients that discontinued due to elevations in hepatic analytes. This was the reason for three of the missed discontinuation cases that I had identified (HMAVA 026-2613, HMBT 106-1610, and HMBT 200-2005). The sponsor's line listing identifies a fourth patient who discontinued for this reason (HMAW 116-4013).

4.2.2.1.1 HMAVA 026-2613

This 64 year old Caucasian female was taking duloxetine 60 mg BID. After having normal baseline LFTs, she manifested abnormal LFTs on laboratory tests drawn on study day 55 with an ALT of 320 and an AST of 202. There was no associated TBILI abnormality. Viral serologies were negative. About one week later the transaminases were in the same range and she discontinued duloxetine. LFTs drawn about three weeks later showed normal transaminase values.

4.2.2.1.2 HMBT 106-1610

This 59 year old Caucasian male was taking duloxetine 60 mg BID for painful diabetic neuropathy. After having nearly normal baseline LFTs, he manifested abnormal LFTs on laboratory tests drawn on study day 54 with an ALT of 250 and an AST of 87. There was no associated TBILI abnormality. Viral serologies were negative. Over the next few weeks the transaminases slowly declined, but the GGT increased; the patient discontinued duloxetine three weeks after the peak ALT occurred. LFTs drawn about two weeks later showed normal transaminase values.

4.2.2.1.3 HMBT 200-2005

This 67 year old Caucasian male was taking duloxetine 60 mg BID for painful diabetic neuropathy. After having a normal baseline TBILI (0.8 mg/dl), his TBILI was remeasured a week later on the day prior to duloxetine initiation. It had increased to 1.4 mg/dl. The patient was instructed to discontinue the duloxetine on day 2 of therapy. The TBILI had increased to 1.5 mg/dl and the unconjugated was 1.2 mg/dl. Two weeks later the TBILI had declined to 0.7 mg/dl. Concurrent transaminases were within normal limits.

4.2.2.1.4 HMAW 116-4013

This 59 year old Caucasian male was taking duloxetine 60 mg daily. He had slightly elevated baseline transaminases, but normal GGT and ALKPH. One month into treatment, he manifested elevated ALKPH (416) and GGT (303); the transaminases had decreased slightly from baseline. There was no associated TBILI abnormality. Two days later the patient discontinued duloxetine. After a few weeks ALKPH had declined but GGT had not. No hepatic work-up was described in the narrative.

4.2.2.2 The AE preferred term was not included in the sponsor's search algorithm

Patient HMBT 302-3202 had an AE with the preferred term "hepatitis". The sponsor states that hepatitis was not included as a search term because "hepatitis is generally used to indicate an infectious etiology".

Despite the sponsor's assertion regarding the meaning of the word "hepatitis", we would consider any AE coded to "hepatitis" to be worth considering in an evaluation of liver-related AEs.

HMBT 302-3202 This 57 year old Caucasian male was taking duloxetine 60 mg BID for painful diabetic neuropathy. After having a normal baseline ALT and AST, he manifested abnormal LFTs on laboratory tests drawn on study day 50 with an ALT of

785 and an AST of 247. There was no associated TBILI abnormality. Four days later the patient stopped taking duloxetine, metformin, and rosiglitazone. Viral serologies were negative. Three days later, the ALT and AST were 467 and 130. About three weeks later the ALT and AST had further declined to 60 and 22.

4.2.2.3 The reason for discontinuation was related to abnormal LFTs, but was coded to a reason other than AE or "other clinically significant lab value"

Lilly did an additional review of the reasons for discontinuation for any patient who discontinued early in order to identify any patients who discontinued for a liver-related abnormality. The search identified three patients who had not previously been identified as discontinuing for a liver-related AE or for "other clinically significant lab values". Of the three patients, Patient HMBT 105-1503 had been previously identified (and is described below in section 4.5.1.3) because he had a liver-related SAE; however, patients SBAV 104-1402 and HMBO 105-1523 are described below.

4.2.2.3.1 SBAV 104-1402

This 62 year old Caucasian female was taking duloxetine 40 mg BID. After having a normal baseline ALT and AST, he manifested abnormal LFTs on laboratory tests drawn on study day 50 with an ALT of 271 and an AST of 96. There was no associated TBILI abnormality. That day the patient stopped taking duloxetine. The ALT and AST were reported to have normalized two weeks later, although the exact values were not included in the narrative.

Reviewer's comment: The stated reason for discontinuation was "sponsor's decision". The 7/7/04 submission states, "It is not clear why this coding was used as this patient clearly had abnormal laboratory values at the time of discontinuation from the study".

4.2.2.3.2 HMBO 105-1523

This 46 year old Caucasian female was taking duloxetine 60 mg BID. After having a normal baseline ALT and AST, she manifested abnormal LFTs on laboratory tests drawn on study day 56 with an ALT of 543 and an AST of 311. About one month prior to the LFT abnormalities, LFTs were within normal limits. The patient then took acyclovir for about one week, but was not taking it for the three weeks prior to the measurement of the abnormal LFTs. There was no associated TBILI abnormality. Four days later the patient stopped taking duloxetine. Viral serologies were negative. Three days later, the ALT and AST were 405 and 236. About seventeen days later, the ALT and AST had further declined to 74 and 46.

Reviewer's comment: The stated reason for discontinuation was "physician's decision". The investigator's comments stated that the "patient discontinued study drug due to high liver enzyme results".

4.2.3 Discontinuations for any liver-related problem identified by a liver related AE, an abnormal LFT result, or a hand's-on search of reasons for discontinuation

The table below shows that within the placebo controlled studies safety database, when all discontinuations related to LFT abnormalities are included, there is a statistically significant excess of discontinuations in the duloxetine group (0.2% [8/4507]) compared to the placebo group (0% [0/3054]). (updated table 6a, p. 10, 7/7/04 submission).

Event	PLACEBO (N=3054) n(%)	DULOX (N=4507) n(%)	Total (N=7561) n(%)	Fishers Exact p-value	CMH p-value
OVERALL	0(0.0%)	8(0.2%)	8(0.1%)	0.025	0.030
Liver function test abnormal	0(0.0%)	4(0.1%)	4(0.1%)	0.153	0.100
Alanine aminotransferase increased	0(0.0%)	2(0.0%)	2(0.0%)	0.518	0.157
Other significant lab values*	0(0.0%)	2(0.0%)	2(0.0%)	0.518	0.367

The table below shows that within the fixed dose study subset, when all discontinuations related to LFT abnormalities are included, there is evidence of a dose-response relationship (updated table 7a, p. 10, 7/7/04 submission).

Event	PLACEBO (N=2148) n(%)	DLX < 40 (N=607) n(%)	DLX 40 (N=177) n(%)	DLX 60 (N=620) n(%)	DLX 80 (N=1319) n(%)	DLX >=120 (N=421) n(%)	TOTAL DULOX (N=3144) n(%)	TOTAL DULOX VS. PLA p-Value Exact (a)
OVERALL	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	2(0.2%)	2(0.5%)	5(0.2%)	.085
Liver function test abnormal	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.1%)	1(0.2%)	2(0.1%)	.518
Other significant lab values*	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	0(0.0%)	1(0.2%)	2(0.1%)	.518
Alanine aminotransferase increased	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.1%)	0(0.0%)	1(0.0%)	1.00

The table below summarizes the incidence of discontinuations related to liver abnormalities in the overall duloxetine exposures dataset, regardless of the method by which the discontinuation was identified or the reason to which it was coded (updated table 10a, p. 11, 7/7/04 submission)[4].

[4] Patient SBAM 403-4204 is described below in 4.3.1.2 regarding a liver-related SAE. The patient discontinued due to "elevated liver enzymes". This discontinuation was not captured in the sponsor's search for any liver-related discontinuation because the database from the open label study during which the discontinuation occurred has not been validated and locked (see pp 3-4, 7/13/04 submission).

Event	DULOX (N=8454) n(%)
OVERALL	27(0.3%)
Liver function test abnormal	10(0.1%)
Alanine aminotransferase increased	5(0.1%)
Other significant lab values*	4(0.0%)
Aspartate aminotransferase increased	2(0.0%)
Gamma-glutamyltransferase increased	1(0.0%)
Hepatic function abnormal NOS	1(0.0%)
Hepatitis NOS	1(0.0%)
Hyperbilirubinaemia	1(0.0%)
Jaundice NOS	1(0.0%)
Transaminases increased	1(0.0%)

4.3 Serious adverse events related to hepatotoxicity

In the placebo-controlled studies database, one placebo patient and one duloxetine patient reported liver related SAEs (preferred terms "alanine aminotransferase increased" and "aspartate aminotransferase increased"). In the fixed dose subset, one placebo patient had a liver related SAE.

In the overall duloxetine exposures database, 0.05% (4/8454) of duloxetine patients reported liver related SAEs. The preferred terms for the SAEs are listed in the sponsor's table below (p. 81, 4/1/04 submission).

Table 11. Liver-Related Serious Adverse Events
MedDra Preferred Terms, By Decreasing Frequency
All Patients Who Received Duloxetine
Overall Duloxetine Exposures Safety Database

Event	DULOX (N=8454) n(%)
PATIENTS WITH >=1 SERIOUS AE	4(0.0%)
Alanine aminotransferase increased	2(0.0%)
Aspartate aminotransferase increased	2(0.0%)
Gamma-glutamyltransferase increased	1(0.0%)
Hepatic function abnormal NOS	1(0.0%)
Jaundice NOS	1(0.0%)
Liver function test abnormal	1(0.0%)

4.3.1 Specific SAEs

Two of the duloxetine treated patients in the overall duloxetine exposures database who had hepatic SAEs are described above in the section updating the cases that met the criteria for Hy's law (3.2).

4.3.1.1 SBAX 703-3105 (placebo)

This patient was a 34 year old Hispanic female treated with placebo who had a serious adverse event with the verbatim term "aspartate aminotransferase increased". Fifty-one days into the trial she had an ALT of 67 and an AST of 48. The AST was reported as being >3x ULN, although by the [ ] reference range table (Table 2, p. 32, 4/1/04

submission), the AST normal range was 9-34. Her baseline ALT and AST were 21 and 23. The patient stopped drug on day 79; the transaminases had normalized.

***Reviewer comment**: Given the mild increase in the patent's transaminases, it is not clear what qualified this adverse event as "serious".*

4.3.1.2 SBAM 403-4204

This patient was a 70 year old Caucasian female being treated with duloxetine 80 mg daily for stress urinary incontinence. About nine weeks into treatment the patient went from normal ALT at baseline, two weeks, and five weeks to a markedly elevated ALT, AST, and GGT; see table below for all hepatic laboratory values. The verbatim term for the patient's SAE was "raised liver enzyme levels". There was no increase in total bilirubin associated with the increase in liver enzymes. The patient was asymptomatic; hepatitis viral serologies were negative, and no other causative factors were identified. The patient was discontinued from duloxetine after a repeat test three days later showed a persistent elevation of LFTs. The patient's LFTs returned to normal within two months.

Date	Visit	ALT (6-34 U/L)	AST (9-35 U/L)	AlkPhos (31-106 U/L)	GGT (4-49 U/L)	T. Bilirubin (0.2-1.2 mg/dl)
	1	15 U/L	28 U/L	69 U/L	20 U/L	0.6 mg/dl
	2	17 U/L	20 U/L	65 U/L	20 U/L	0.8 mg/dl
	3	15 U/L	20 U/L	68 U/L	23 U/L	1.0 mg/dl
	4	1038 U/L	654 U/L	90 U/L	80 U/L	0.8 mg/dl
	4a-RETEST	862 U/L	451 U/L	90 U/L	95 U/L	0.9 mg/dl
	4b-RETEST	546 U/L	246 U/L	87 U/L	91 U/L	0.8 mg/dl
	4c-RETEST	49 U/L	31 U/L	81 U/L	64 U/L	0.7 mg/dl
	41-RETEST	17 U/L	23 U/L	83 U/L	41 U/L	0.4 mg/dl

***Reviewer comment**: Despite the striking increase in the patent's transaminases, it is not clear what qualified this adverse event as "serious".*

4.3.1.3 HMBT 105-1503

This patient was a 75 year old Caucasian male who was treated with duloxetine 120 mg q day for painful diabetic neuropathy. The patient did not tolerate the drug very well, and a decision was made to discontinue it about nine weeks into treatment[5]. The patient tapered duloxetine over ten days and the early termination visit labs showed an elevated AST, ALT, GGT, ALKPH, and CPK; see table below for values. He was reported as having an SAE "liver dysfunction" coded to "Hepatic function abnormal NOS".

[5] The reason for study discontinuation was documented on the CRF as "personal conflict or patient decision", with an added comment of "multiple adverse events".

F1J-MC-HMBT 105-1503/L1

DATE	Visit	AST	ALT	CPK	AlkPh	GGT	Bili	Hep A	Hep B	Hep C
	1	25	38	**514**	65	38	8			
	2	24	42	416	67	40	7			
	5	22	46	304	81	47	5			
	7	**80**	**167**	**797**	**284**	**830**	11	Neg	Neg	Neg
	501L	47	**133**	143	**313**	**947**	12			
	502L	56	**122**	167	**348**	**1019**	10			
	503L	42	92	128	**304**	**939**	10			
	504L	35	65	179	**243**	**761**	12			
	505L	27	26	101	**222**	**499**	5			
[ ]	Hospital	25	35	n/a	141	**230**	n/a			
[ ]	Hospital	21	41	n/a	108	162	n/a			
	508L	29	27	**459**	72	76	5			

It should be noted that the patient had started perhexeline about three months prior to starting duloxetine, and there was some suspicion that the LFT abnormalities could have been related to that drug. The patient was hospitalized 19 days after the last dose of duloxetine for persistently abnormal LFTs and a right leg cellulitis. Perhexeline was discontinued at this time. Following the hospitalization, the patients ALT and AST normalized, although it took longer for his ALKPH and GGT to normalize. Total bilirubin stayed within the normal range through the course of the adverse event.

Reviewer comment: *The picture of laboratory abnormalities in this case is not consistent with the transaminitis observed in other examples of duloxetine-associated hepatotoxicity. Perhexiline has also been associated with a hepatotoxicity that mimics alcoholic hepatitis.*

4.4 15-day Reports

Because six months have elapsed since Lilly submitted the response to the second approvable letter, we requested that they send any 15 day reports for liver-related adverse events (identified using the same search terms as above) from unblinded studies that have been submitted to any duloxetine IND or NDA since the 12/22/03 submission. Two 15-day reports were submitted.

4.4.1 US_0405103141 (Patient SBCD 084-1661)

A 65 year old Caucasian female was in an open label study for SUI. She was treated with duloxetine 40 mg daily for about one month when she was hospitalized for fever, nausea, rash, and elevated ALKPH. She had the following lab values on admission: ALKPH 664, TBILI 0.5 mg/dl, ALT 214, AST 128, and WBC 13.8. A RUQ ultrasound showed

hepatomegaly, but no cholelithiasis or cholecystitis. The next day the patient's ALKPH (566) and ALT (156) had decreased somewhat, but the WBC increased (15.9). Due to the patient's abdominal pain, a HIDA scan of the gall bladder was also performed; it was negative. Duloxetine was not discontinued. No additional information was available in the 15 day report, other than the patient was being treated with antibiotics.

Reviewer comment: This serious adverse event does not appear to be a case of an isolated severe liver injury. The combination of the elevated ALKPH along with the abdominal pain and the elevated WBC is more suggestive of an infection in the biliary tree.

4.4.2 JP_040603589

A 35 year old Japanese male with a history of alcoholic hepatopathy was treated with duloxetine for major depressive disorder, recurrent episode as part of study 0312 A2027. His baseline LFTs were AST 62, ALT 103, and GGTP 1473. After being treated with duloxetine three capsules daily (no dosage strength included in the report) for two weeks, the patient's alcoholic hepatopathy reportedly exacerbated, and the patient requested to terminate the study prematurely. On that date his LFTs were AST 158, ALT 113, and GGTP 3540. The patient was taking zopiclone concomitantly. Information on the extent of the patient's alcohol intake was not available.

5 Consultant reports

5.1 [redacted]

Dr. — reviewed the liver function test data as well as the narrative summaries for patients meeting the modified Hy's rule criteria. His conclusions follow below:

- The role of duloxetine in the individual cases can not be ruled out; however, all are "highly confounded by either alcohol and/or other potential hepatotoxins."
- Duloxetine appears to have a "reasonably safe" hepatic profile with no obvious signals for hepatotoxicity based on a modified Hy's Rule.
- The proposed labeling is "overly cautious" in that it states that "duloxetine should be avoided in anyone with hepatic impairment, based solely on the PK data. He favors labeling that recommends using duloxetine "with caution" in patients with cirrhosis, rather than contraindicating it.

5.2 [redacted]

Dr. — commented on three issues: the increase in AUC in patients with cirrhosis, the overall pattern of aminotransferase elevations, and the specific cases of hepatotoxicity.

- Dr. — does not agree with the FDA's request (based on the date of the consultation letter, this request would have come from the approvable letter from HFD-580) to exclude patients with any degree of hepatic insufficiency from using duloxetine. He recommends that the wording regarding patients with liver disease be more similar to language used for SSRIs.
- Dr. — observes that the duloxetine treated groups had a "small increase" in the percentage of patients having an increase from baseline exceeding 3X ULN for

AST/ALT compared to the placebo groups. He noted that for many patients, the transaminases normalized while patients stayed on their duloxetine. Regarding labeling, he suggested that the package insert mention transient elevations of transaminases and suggest that duloxetine be discontinued if the elevations should exceed 5x or 10x ULN.

- Regarding the four cases of serious liver injury, Dr. — considered only the Canadian case (Pt HMAW 500-5254, see section 3.2.2 above for details) as being possibly related to duloxetine. In Dr. — opinion, the high initial AST/ALT, the histologic picture (based in his own review of the liver biopsy slides), the positive dechallenge, and the lack of an alternative explanation support the role of duloxetine in this case. Not supporting the drug as the "culprit" was the onset of liver injury seven months into therapy, and the emergence of the jaundice following alcohol binges by the patient. Dr. — notes, however, that the diagnosis is not simply alcoholic hepatitis (based on the AST/ALT pattern and histologic findings).
- In addition to the above comments about the transaminase labeling language, Dr. — recommends that the labeling include some discussion of the uncertainty about the interaction of duloxetine and heavy alcohol intake. He does not think that further pre-market testing of this potential interaction is warranted, but does recommend that any cases of hepatotoxicity occurring in the postmarketing period be reviewed by a data safety monitoring board to identify any problems early.

5.3 [redacted]

Dr. [redacted] reviewed each of the four cases of liver injury occurring in duloxetine treated patients provided by the sponsor. He concluded that duloxetine may have contributed to the hepatic injury in patient A06706, but thought it unlikely given the alcohol history and confounding factors (polypharmacy and fatty liver). Although he did not make a causality assessment for patient A09505 because of the unknown nature of some of the substances he was taking, he did not think that the rapid rise and fall in the transaminases was suggestive of a toxic hepatitis. Dr. [redacted] concluded that the liver biopsy, laboratory abnormalities, and history of heavy alcohol use of patient HMAW 500-5254 supported a diagnosis of alcoholic hepatitis superimposed on chronic liver disease. "Duloxetine was not the cause of nor did it contribute to the hepatitis in this case," he stated. Patient HMBT 305-3512's hepatic abnormalities were most consistent with symptomatic choledocholithiasis and "not likely related to Duloxetine treatment".

Dr. — raises the concern that the phospholipidosis observed in preclinical studies may be problematic for patients already at risk for fatty liver disease, such as patients with diabetes. Additionally, patients with impaired liver function at baseline are at risk for exposure to high duloxetine levels, due to the altered metabolism of duloxetine in those patients.

Dr. — concludes that duloxetine is not likely to be the cause of significant hepatotoxicity, but he feels that the risk of hepatic impairment associated with duloxetine in patients with diabetes has not been assessed adequately for him to make an assessment of the risk in this group. He recommends continuing to monitor liver function in clinical

trials, especially in those patients with diabetes. He recommends comparing the rate of liver function abnormalities and adverse events in patients with preexisting hepatic impairment to those without. Additionally, he recommends studying safety, tolerability and pharmacokinetics of duloxetine in patients with chronic liver disease who do not have cirrhosis; his recommendation comes from his concern that physicians will use duloxetine in patients who have unrecognized liver disease, so the safety should be characterized in that population.

5.4 [ ]

Dr. [ ] responded to several questions posed to him by Lilly regarding duloxetine hepatotoxicity.

- *How would you characterize the hepatic safety profile of duloxetine?*
- *What specifically do you think of the four cases?*

Regarding the hepatic safety profile, Dr. [ ] concluded that there appeared to be some evidence of duloxetine-related hepatotoxicity, but that it resolved with time while the patients stayed on drug. Thus he characterized the safety profile as "good". Regarding the specific cases (4 on duloxetine, 2 on placebo), he characterized two as having the suggestion of being "duloxetine-associated" hepatitis; one of the patients was actually on placebo (HMBH-120-3017). The other patient was A09505 from a [ ] study.

- *How do you think duloxetine[should] be used in patients with diminished metabolism, such as hepatically impaired patients?*
- *We do not think that duloxetine should be contraindicated in patients with severe hepatic failure nor that the dose should be reduced in mild and moderately impaired hepatically impaired patients, do you agree?*

Dr. [ ] suggested that in hepatically impaired patients, it would be reasonable to give duloxetine at a lower dose than that intended for healthy patients because there is significant first pass metabolism and it is highly protein bound. He did not think duloxetine should be contraindicated in patients with hepatic impairment; however, the dose should be started low and increased cautiously.

- *Are routine blood tests helpful in detecting those with a duloxetine-induced hepatitis?*

Dr. [ ] did not think that routine monitoring of liver function was necessary except "perhaps in those with an excessive intake of alcohol."

5.5 [ ]

Dr. [ ] was asked only to review the case of patient HMAW 500-5254. As described above and in my previous review dated (9/22/03), this patient had a case of severe liver injury involving a total bilirubin that exceeded the upper limit of normal 30-fold. Dr. [ ] reviewed the patient's clinical history, laboratory data, and liver biopsy. He characterized the patient's clinical picture as acute hepatitis superimposed on chronic liver disease. He concluded that both the acute hepatitis and the chronic liver disease

were due to alcoholism. The diagnosis of chronic liver disease were supported by a clinical history of alcoholism, physical examination findings (e.g., ascites, telangiectasias), and histologic findings on the liver biopsy (e.g., pattern of fibrosis).

Dr. [ ] did not think there was reason to implicate duloxetine in the development of the patient's cirrhosis, given that drug induced cirrhosis generally follows years of administration of a drug and often has an association with autoimmune phenomena. Additionally, he did not think that based on a probability assessment (e.g. time to onset, exclusion of other causes of liver disease, consistency with other evidence, and response to withdrawal), duloxetine was a likely cause of the acute hepatitis. In particular he noted that most patients who had a hepatotoxic reaction to duloxetine had it early (within the first 3 months) whereas this patient had relatively normal LFTs until the acute onset of hepatitis seven months into treatment.

5.6 [ ]

Dr. [ ] served as a consultant to Lilly over a few years. His letter dated November 20, 2003 summarized his views on abnormal liver function associated with duloxetine treatment.

1. The cases of hepatotoxicity associated with duloxetine were mainly hepatocellular in nature and generally reversible (where follow-up information was available).
2. Of the four cases of severe liver injury in the duloxetine development program, he considers that duloxetine may have had a deleterious effect in three.
3. Hepatotoxicity with duloxetine appears to be due to an idiosyncratic reaction as opposed to an immune reaction or "toxic" metabolites.
4. Metabolism of the parent drug is decreased in the presence of underlying cirrhosis. Dr. [ ] addressed the concern of whether patients with underlying liver disease are more prone to adverse liver effects from duloxetine. In his analysis, patients with abnormal baseline ALT were about twice as likely as those with normal baseline ALT to have an increase in ALT of 100 units. He concludes that although liver injury may be enhanced by duloxetine exposure in patients with liver disease, the severity is not worsened.
5. Dr. [ ] raises the issue of whether patients with preexisting liver disease should be treated with a lower dose of duloxetine, or not at all. Although he does not present a clear answer to these questions, he suggests that it might be worth monitoring the LFTs of such patients for the first six months of treatment in the postmarketing period.

5.7 [ ]

After reviewing the data on duloxetine, Dr. [ ] described two liver reactions occurring in the duloxetine development program. The first type is a small and transient elevation in transaminases and alkaline phosphatase that occurred in about 1% of patients treated with duloxetine in placebo controlled trials. Due to the small magnitude of the LFT abnormalities and the transient nature, he did not think it necessary to monitor LFTs.

He also noted the more severe pattern of liver injury observed in the four patients discussed earlier (and in detail in my review of the prior response to the AE letter). Similar to other consultants, he could not rule out the role of duloxetine in the liver injury of three of the four patients, although he considered each of the three to be confounded in some way. Given the rarity of these severe liver reactions, the late occurrence in two of the cases (20 and 32 weeks), and the uncertainty about their relationship to duloxetine, again Dr. [ ] does not recommend regular LFT monitoring.

With regard to patients with preexisting liver disease (as represented by six patients with moderately severe cirrhosis given a single dose of duloxetine), Dr. [ ] recommends cutting the duloxetine dose in half for the treatment of depression in those patients. He recommends studying the PK of duloxetine in patients with less severe liver dysfunction as he believes they would be the patients more likely to receive duloxetine treatment.

5.8 [ ]

Dr. [ ] concluded that duloxetine may have played a role in the severe liver injury in three of the four cases that fulfilled Hy's rule, although each of those cases had other factors which may have influenced the development of hepatotoxicity (e.g. alcohol abuse, concomitant medications associated with hepatotoxicity).

Regarding patients with chronic liver disease, Dr. [ ] recommended that the duloxetine dose should be reduced, but did not think it needed to be contraindicated.

Dr. [ ] also recommended that patients with a moderate increase of transaminases should be assessed for use of alcohol or other drugs known to be associated with hepatotoxicity. If that relationship is identified, alcohol use should be avoided with duloxetine.

Finally, Dr. [ ] suggests that monitoring ALT and AST at 15-30 days after initiation of duloxetine may help prevent more severe adverse effects in liver function.

5.9 Summary of Consultant Conclusions

Of the eight consultant reports, seven commented on all aspects of the hepatotoxicity issue with duloxetine, while one had comments limited to the evaluation of Patient HMAW 500-5254.

Topics that the seven broader consultants commented on

- Involvement of duloxetine in severe liver injury cases
    - The general consensus was that Patient HMBT 305-3512 passed a common bile duct stone, and that her case did not represent duloxetine-related hepatotoxicity.
    - Regarding the other three cases that met the ALT and TBILI criteria for modified Hy's law cases, most of the consultants concluded that a role for duloxetine in the severe liver injury could not be ruled out, but that the

presence of multiple confounding factors made a role for duloxetine less likely.
    - Drs. [ ] concluded that patient HMAW 500-5254's severe liver injury was fully attributable to alcohol abuse, and duloxetine played no role.
- Recommendation for dosing in hepatically impaired patients
    - No consultant supported the contraindication of duloxetine in patients with hepatic impairment.
    - Some consultants recommended halving the duloxetine dose in patients with hepatic impairment
    - Some consultants recommended that labeling include some discussion of the uncertainty about the interaction of duloxetine and heavy alcohol intake
- Need for additional study in hepatically impaired patients
    - Some consultants recommended studying the safety, tolerability and pharmacokinetics of duloxetine in patients with mild hepatic impairment without cirrhosis, as these patients may be at risk and may not have been identified as having hepatic impairment prior to treatment.
    - Other suggestions included regular LFT monitoring of patients with heavy alcohol intake, monitoring patients with preexisting liver disease for the first six months, monitoring all patients around 2-4 weeks of treatment, having a data safety monitoring board review all cases of hepatic dysfunction reported in the postmarketing period
- Other
    - Dr. [ ] expressed concern that the hepatic safety profile had not been adequately studied in patients with diabetes. He expressed concern that the phospholipidosis observed in preclinical studies may represent a risk for fatty liver

6 Discussion

No additional Hy's law cases have been reported in duloxetine-treated patients since my review of the response to the 2nd approvable letter (dated 9/22/03). The LFT analyses included in the sponsor's safety update, as well as in response to my data requests, show that there remains an excess of important ALT elevation in patients taking duloxetine. There was a small but statistically significant excess of discontinuations due to liver-related adverse events in the duloxetine group compared to the placebo group (0.2% [8/4507] vs. 0% [0/3504]). Overall, about 0.3% of duloxetine treated patients discontinued due to liver-related adverse events (27/8454). In the full cohort of placebo controlled trials of duloxetine in any indication, 1% (39/3732) of duloxetine treated patients had a $\geq$ 3x the upper limit of normal elevation of ALT compared to 0.2% (6/2568) of placebo treated patients. Among the subset of placebo-controlled studies using a fixed dose design, there was evidence of a dose-response relationship for ALT elevation $\geq$ 3x the upper limit of normal.

The hepatology consultants employed by the sponsor had somewhat differing interpretations of the jaundice case (HMAW 500-5254), with some concluding that there

was no role of duloxetine and others concluding that there was. In general they seemed to agree on the role of duloxetine in the other Hy's law cases (the female having a common bile duct stone, and the other two possibly having a role of duloxetine, but being confounded by other factors including alcohol and other medications). There was general agreement that restricting use of duloxetine in patients with any degree of hepatic impairment was too stringent. Several recommended further study of the safety and tolerability of duloxetine in a population of patients with mild hepatic impairment, so that it could be used more rationally in that population.

In my prior review I concluded that a Precautions statement would be appropriate to describe the risk of transaminase elevation and liver injury associated with duloxetine. However, while reviewing the current submissions, I have reflected further on the appropriate placement of a cautionary statement. It seemed to be useful to look at other antidepressants that are associated with liver dysfunction. During the NDA review of mirtazapine, it was observed that 0.9% (26/2796) of mirtazapine treated patients discontinued prematurely or had an SAE due to LFT abnormalities compared to 0.3% of placebo treated patients (2/605). Additionally, 1.9% (8/424) of mirtazapine treated patients had an ALT>3xULN compared with 0.3% (1/328) of placebo treated patients. There were no patients who had a TBILI that exceeded 2 mg/dl. Based on reading Dr. John Balian's (the original medical reviewer) discussion of hepatotoxicity in the mirtazapine development program (review dated 10/19/1995), as well as Dr. John Senior's hepatology consultant review (dated 10/12/95), there did not appear to be any cases that met the Hy's law criteria. The mirtazapine labeling contains the following Precautions statement:

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® SolTab® should be used with caution in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Another pertinent antidepressant to consider is nefazodone. During the NDA review of nefazodone, it was observed that there were no cases of hepatic failure attributed to nefazodone and there did not appear to be any cases that met the Hy's law criteria (although this was not explicitly stated); 0.5% (11/2256) of nefazodone treated patients discontinued prematurely for LFT abnormalities compared to 0.3% of placebo treated patients (2/672)[6]. In the short term placebo controlled trials, 1.4% (23/1680) of nefazodone treated patients had an ALT>3xULN compared with 0.6% (7/1095) of placebo treated patients[7]. With regard to LFT abnormalities, the original package insert mentioned abnormal LFTs as infrequent and hepatitis as rare (in the adverse reactions section). However, subsequently during the postmarketing period, it was observed that there was a reporting rate of liver failure associated with nefazodone use that was 3-5 times the background rate in the general population. In December 2001, a black box

[6] See Dr. Jerry Boehm's review dated 1/13/99.
[7] See Dr. Jerry Boehm's review dated 5/6/99.

warning was added to the nefazodone PI to warn prescribers of the risk of liver failure resulting in death or transplant associated with nefazodone.

In the above two examples, there are similar findings based on the NDA safety database (i.e., a signal for drug-induced transaminase elevation, without evidence of associated severe liver injury); however, the postmarketing experience differs. Nefazodone was identified as having an elevated risk of hepatic failure based on postmarketing data. Considering the premarket experience with duloxetine in comparison, which is substantially larger in size than mirtazapine and nefazodone, we observe that duloxetine also increases transaminases in a subset of patients (that in some cases resolved spontaneously while the drug was continued). Duloxetine differs, however, in that during clinical development there were also three cases that reached the Hy's law thresholds for ALT and TBILI. Notably, these three cases were all confounded to some degree (all associated with ethanol intake, and evidence of ALKPH abnormalities as well). Typically, in cases of drug-induced severe liver injury, ALKPH and GGT are within normal limits (or at least not markedly abnormal). The presence of ALKPH and/or GGT abnormalities at baseline in the two Japanese patients, and the substantial increase in ALKPH and/or GGT in all three patients suggest that some other process (e.g., obstruction) may have been going on other than (or in addition to) duloxetine-induced liver injury. However, it should also be noted that as documented in my 9/22/03 memo, other recent development programs for antidepressants have not had the type of liver injury cases that occurred in the duloxetine development programs (i.e., exacerbation of liver dysfunction associated with heavy alcohol intake without the transaminase pattern typical of alcoholic hepatitis [AST>2x ALT]).

At this point in time, I do not think the deleterious effects of duloxetine on the liver should preclude approval if it is determined that it is efficacious, and there are no other safety issues that preclude approval. However, the package insert should contain a [redacted] statement that cautions prescribers about the risk of potential liver injury, particularly in patients who are heavy users of ethanol. The [redacted] should recommend abstinence from ethanol ingestion during duloxetine therapy. Furthermore, duloxetine-treated patients will need to be followed closely in the postmarketing period to monitor for any change in the pattern of liver injury or the emergence of a signal larger than what is observed in the development program. Finally, as suggested by some of Lilly's hepatology consultants, it would be helpful to study the safety and tolerability of duloxetine in a population of patients with mild hepatic impairment, so that it could be used more rationally in that population.

7 Proposed labeling

Lilly has provided counterproposals to some of DNDP's proposed labeling regarding hepatotoxicity. In this section I will first place DNDP's proposal in 10 point font and then provide Lilly's comments beneath in italics.

Clinical Pharmacology, Special Populations subsection:

Hepatic Insufficiency — Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and elimination. After a single 20 mg dose of duloxetine, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although Cmax was similar to normals in the cirrhotic patients, the half-life was about 3 times longer (*see* PRECAUTIONS). It is recommended that duloxetine not be administered to patients with mild, moderate, or severe hepatic insufficiency (*see* DOSAGE AND ADMINISTRATION).

In place of the highlighted language above, Lilly proposed '[ ] hepatic insufficiency.

Reviewer comment: DNDP has previously conveyed to Lilly that "mild, moderate, or severe hepatic insufficiency" is the standard language used in labeling. Lilly offered their counterproposal because of their market research that indicates that clinicians do not understand the distinction between those degrees of hepatic insufficiency. This reviewer suggests that the most straightforward language in this case would be to say "that duloxetine not be administered to patients *any* hepatic insufficiency".

[

]

Lilly's proposed the following edits to the above paragraph:

- The subsection under Precautions-General would be called '[ ]" with two subsections within it called [ ]
- Lilly disagreed with DNDP's characterization of the four reported cases as [ ]' given that only one case had jaundice and clinical symptoms. As such, they proposed describing only that one case in the separate [ ] subsection. The other three cases that met Hy's rule (ALT >3x ULN and Total bilirubin >2 mg/dl, without evidence of obstructive disease) would be described within the '[ ]' subsection
- Lilly proposes including more of the clinical scenario for the patient who developed clinically symptomatic liver injury
- Lilly proposes deleting the sentence [ ] because they do not believe that there is sufficient evidence to support that statement. However, they do propose the following statement,[ ]

Reviewer comment: I concur with the deletion of the statement [ ]' because it is conjecture and, in fact, it may

be that it is the other way around ([redacted]

Based on my review of the data submitted by Lilly in the response to the second approvable letter and their subsequent responses to my data requests, and consideration of their current labeling proposal, I have the following proposal:

Hepatotoxicity

Liver transaminase elevations resulted in patient discontinuation in 0.3% (27/8454) of duloxetine treated patients. [redacted]

[redacted]

Precautions, Use in Patients with Concomitant Illness

[redacted]

Lilly proposes inserting the words [redacted] in front of [redacted] in the above sentence.

Reviewer comment: The proposed insertion appears to be designed to fit with the language they propose above for the "Special Populations" section of the Clinical Pharmacology section. However, it seems unnecessary and potentially confusing.

Precautions, Information for Patients

[ ]

Lilly proposes deleting the highlighted text above because they do not consider it informative for the patient. I agree that it could be removed, but I will defer to the OCPB reviewer on this issue.

Precautions, Drug Interactions

Duloxetine May Have a Clinically Important Interaction with the Following Other Drugs:
Alcohol — When duloxetine and ethanol were administered several hours apart so that peak concentrations of each would coincide, duloxetine did not increase the impairment of mental and motor skills caused by alcohol. [

]

[ ]

Reviewer comment: Lilly proposes changes to the second paragraph above that are similar to those proposed for the general Precautions statement. My proposal follows below:

[ ]

Dosage and Administration, Special Populations

Dosage for [ ] Impaired Patients —[

]

Again, Lilly proposes replacing "mild, moderate, or severe" with [

] " hepatic insufficiency. For the same reasons stated above, I would keep our current language, or replace "mild, moderate, or severe" with "any".

8 Evaluation of CPK abnormalities in the duloxetine development program

While I was examining the narratives for the individual cases of liver-related adverse events leading to discontinuation, I noticed that a few patients had elevations of their CPK. Because a lot of data has been collected on duloxetine since the review of the

original NDA submission for duloxetine in the treatment of MDD, I thought it prudent to examine the incidence of CPK outliers and AEs related to elevated CPK that had occurred in the duloxetine development program. See Appendix 2 (section 9.2 for the specific requests).

8.1 Mean change from baseline analysis

As seen in the table below, there was evidence of an increase in the mean change from baseline to endpoint and maximum in the duloxetine group compared to the placebo group (Table 3a, p. 9, 6/30/04 submission).

FDA Table 7. Mean change from baseline to endpoint and maximum value by treatment group, all placebo controlled studies database, patients with normal baseline values.

	Duloxetine (all doses)		Placebo	
	End	Maximum	End	Maximum
CPK (U/L)	10.0	30.8	-4.5	18.3
	(n=4200)		(n=2873)	

In the mean change from baseline analysis that included only fixed dose studies, there was no evidence of a dose-response relationship.

8.2 Outlier analysis

FDA Table 8. Percentages of CPK outliers by treatment group, all placebo controlled studies database, patients with normal baseline values.

	Duloxetine (all doses)				Placebo			
	2x (%)	3x (%)	5x (%)	10x (%)	2x (%)	3x (%)	5x (%)	10x (%)
CPK (U/L)	1.6	0.9	0.5	0.1	1.6	0.6	0.2	0.2
	(n=3718)				(n=2552)			

FDA Table 9. Percentages of CPK outliers by treatment group, all placebo controlled studies database, fixed dose subset, patients with normal baseline values.

Treatment Group	2xULN (%)	3xULN (%)	5xULN (%)	10xULN (%)
Placebo (N=1769)	1.5	0.6	0.1	0.1
DLX<40 (N=514)	1.6	0.6	0.2	0
DLX=40 (N=144)	3.5	2.1	0	0
DLX=60 (N=473)	2.8	2.1	1.3	0.4
DLX=80 (N=1088)	1.4	0.8	0.6	0.1
DLX>=120	2.2	0.8	0.3	0

(N=1088)				

Although there is a slight excess of patients with a CPK value exceeding 3x ULN and 5x ULN in the duloxetine group, there is no evidence of a dose response relationship.

8.3 Abnormal CPK-related AEs

8.3.1 Scope of search algorithm

The following search terms were included in Lilly's search for AEs related to abnormal CPK:

Terms suggested by FDA:
Rhabdomyalysis[8] (sic), myopathy, myalgia, muscle aches, muscle cramps (preferred term: muscle cramp), increased CPK (preferred term: blood creatine phosphokinase increased), abnormal CPK

Terms added by Lilly:
Muscle stiffness, muscle tightness, pain (NOS), musculoskeletal stiffness, muscle rigidity, hypertonia

8.3.2 Discontinuations due to abnormal CPK-related AEs and Serious AEs related to abnormal CPK

In the placebo-controlled studies database, 0.1% of placebo patients (3/3054) and 0.04% (2/4507) of duloxetine patients discontinued for abnormal CPK-related AEs (p. 35, 6/3/04 submission).

Table 5c. Discontinuations due to Abnormal CPK-Related Adverse Events
All Randomized Patients
All Placebo-Controlled Studies Safety Database

	PLACEBO (N=3054) n(%)	DULOX (N=4507) n(%)	Total (N=7561) n(%)
Event			
OVERALL	3(0.10%)	2(0.04%)	5(0.07%)
Blood creatine phosphokinase increased	1(0.03%)	1(0.02%)	2(0.03%)
Muscle cramp	0(0.00%)	1(0.02%)	1(0.01%)
Muscle stiffness	1(0.03%)	0(0.00%)	1(0.01%)
Pain NOS	1(0.03%)	0(0.00%)	1(0.01%)

In the "all placebo-controlled studies" database, there were no AEs related to abnormal CPK that qualified as "serious".

[8] Lilly originally searched their AE database using "rhabdomyalysis", an incorrect spelling of rhabdomyolysis, and did not identify any cases. However, once they were notified of the incorrect spelling, they rechecked the database and there were no instances of rhabdomyolysis.

In the overall duloxetine exposures database, 0.1% (9/8454) of duloxetine patients discontinued due to abnormal CPK-related AEs. The preferred terms for which patients discontinued are listed in the sponsor's table below (p. 41, 6/3/04 submission).

Discontinuations Due to Abnormal CPK-Related Adverse Events
All Duloxetine Patients
Overall Duloxetine Exposures Safety Database

Event	DULOX (N=8454) n(%)
OVERALL	9(0.1%)
Blood creatine phosphokinase increased	2(0.0%)
Myalgia	2(0.0%)
Pain NOS	2(0.0%)
Muscle cramp	1(0.0%)
Muscle stiffness	1(0.0%)
Muscle tightness	1(0.0%)

In the "overall duloxetine exposures" database, there was one AE related to abnormal CPK that qualified as "serious". The preferred term was "pain NOS" and the verbatim term was "aches". However, there was no abnormality of CPK concurrent with this SAE.

8.3.2.1 Specific abnormal CPK-related AEs leading to discontinuation

The search conducted by the sponsor to identify abnormal CPK related AEs identified some muscle-related adverse events. On further questioning of the sponsor to provide the CPK values drawn around the time of these muscle related events, no abnormal CPK values were identified.

Below I describe only the AEs in detail in which CPK was abnormal (usually coded as "blood CPK increased").

8.3.2.1.1 HMATA 010-1922 "Blood CPK increased"

This patient was a 28 yo Hispanic male who had normal CPK at baseline (118). One month into duloxetine therapy (40 mg BID) her CPK had increased to 3246. The duloxetine was stopped, and five days later the CPK had declined to 364. The patient was rechallenged with duloxetine; one week after reinitiating duloxetine, the CPK became elevated again (to 2658). Duloxetine was discontinued immediately, and ten days later the CPK had declined to 516. Three weeks later the CPK had normalized. The narrative noted that no risk factors for CPK increase were present (e.g., no change in exercise pattern, no injury).

Reviewer comment: The positive rechallenge is persuasive in suggesting a causative role for duloxetine in this patient's elevated CPK.

8.3.2.1.2 SBAX 401-1813 "Blood CPK increased"

This patient was a 41 yo Caucasian female who had a mildly elevated CPK at baseline (457, nl range 19-265). 52 days into placebo therapy her CPK had increased to 2162. The patient was discontinued from treatment about two weeks later. No follow-up CPK values were provided.

8.3.2.1.3 HMAYB 146-5643 "Blood CPK increased"

This patient was a 54 yo Caucasian female who had normal CPK at baseline (128). Eight weeks into duloxetine therapy (60 mg BID) her CPK had increased to 672. The CPK stayed in that range (and slightly higher, up to 706) over the next five weeks. At that point the patient was discontinued from duloxetine. One week later the CPK continued to increase (883). No subsequent CPK values were obtained. The narrative noted that the patient began exercising regularly at the beginning of the trial.

8.4 Discussion of CPK-related abnormalities

Although there is a small mean increase in CPK for duloxetine treated patients compared to placebo treated patients, there is no consistent pattern of an excess of CPK outliers and CPK-related adverse events in the duloxetine group compared to the placebo group.

I recommend that the preferred term "blood CPK increased," that occurred in patients treated with duloxetine, be reflected in the "laundry list" in the adverse events section.

9 Appendices

9.1 Appendix 1: Reviewer questions sent to Lilly 3/15/04

Duloxetine Safety Update- Liver Review

Questions for Lilly:

- Please provide the definition for "abnormally high values" for each of the analytes in Table 5.3 (i.e., ALKPH, ALT, AST, GGT, T.BILI).
- Why is the number of placebo patients with ALT values in Table 5.3 (N=1876) different than the number of placebo patients with ALT values in Table 5.5 (N=2563)?
- Similarly, why is the number of duloxetine patients with ALT values in Table 5.3 (N=3687) different than the number of duloxetine patients with ALT values in Table 5.5 (N=3700)?
- How was "normal' at baseline defined for T.BILI and ALKPH?
- Of the studies listed in the "all placebo-controlled studies safety database", please list those that employed a fixed dose design.
    - Using the group of placebo-controlled studies that employed a fixed dose design, please conduct the following analyses:
        - Hepatic laboratory analytes-change from baseline to endpoint, all randomized patients with normal baseline values (similar[9] to table 5.1)
        - Hepatic laboratory analytes-change from baseline to maximum, all randomized patients with normal baseline values (similar[10] to table 5.2)
        - Hepatic laboratory analytes-treatment emergent abnormally high ALT values at anytime, by dose, all randomized patients with normal baseline values (using the same thresholds and format as table 5.5)
- For the "all placebo-controlled studies safety database", please provide the frequency of discontinuation due to liver-related AEs for the duloxetine and placebo groups.
    - Please provide narrative summaries for patients who discontinued due to liver AEs
- Using the group of placebo-controlled studies that employed a fixed dose design, please provide the frequency of discontinuation due to liver-related AEs for the duloxetine (total and broken out by dose group) and placebo groups.
- For the "all placebo-controlled studies safety database", please provide the frequency of liver-related SAEs for the duloxetine and placebo groups.

[9] I am saying "similar" here because I am requesting the same table format as Table 5.1, but the population I am requesting is those patients with normal baseline values (not all randomized patients)

[10] I am saying "similar" here because I am requesting the same table format as Table 5.2, but the population I am requesting is those patients with normal baseline values (not all randomized patients)

- Please provide narrative summaries for patients who had liver-related SAEs

- Using the group of placebo-controlled studies that employed a fixed dose design, please provide the frequency of liver-related SAEs for the duloxetine (total and broken out by dose group) and placebo groups.
- For the "Overall Duloxetine Exposures Database", please provide the frequency of discontinuation due to liver-related AEs and the frequency of SAEs for the duloxetine group.
    - Please provide narrative summaries for patients who had liver-related SAEs or discontinued due to liver-related AEs (include only those narratives that were not included with the "all placebo-controlled studies safety database")

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9.2 Appendix 2: Reviewer questions sent to Lilly 5/25/04

Follow-up questions regarding Duloxetine liver submissions 12/22/03 and 4/1/04:

1a. Please provide tables similar to "updated table 5.5" (All randomized patients with normal baseline values, all placebo controlled studies safety database) for the other liver related analytes (AST, ALKPH, TBILI, and GGT). You can report the incidences for just the treatment groups PBO and ALL DLX.

1b. For the fixed dose design subset of the "all placebo controlled studies safety database", please provide the same tables as requested in 1a, but report all treatment groups (PBO, <40 DLX, 40 DLX, 60 DLX, 80 DLX, ≥120 DLX).

2. Please provide a list of the preferred terms that were used to search for liver-related SAEs and AEs leading to discontinuation.

3a. Please provide a line listing[11] for each of the 19 patients in the "Overall Duloxetine Exposures Database" who discontinued for a hepatic related AE (Table 10, p. 79, 4/1/04 submission). When I counted the narratives included in the Patient Narrative Summaries in the Appendix of the 4/1/04 submission, I only found narratives for sixteen patients.

3b. Please provide a line listing for each of the four patients in the "Overall Duloxetine Exposures Database" who reported a hepatic related SAE. In the Patient Narrative Summaries in the Appendix of the 4/1/04 submission, I only found narratives for SAEs in three patients; two were treated with duloxetine. At the end of the patient narratives, there were summaries for two additional patients (HMAW 500-5254 and HMBT 305-3512) who have been reported previously as having hepatic related SAEs. Are these two additional summaries supposed to bring the total up to four liver-related SAEs in duloxetine treated patients?

4. There is some inconsistency between the patients included in the Patient Narrative Summaries section of the Appendix to the 4/1/04 submission and reports of discontinuation/SAE included in the abbreviated study reports submitted with the 12/22/03 submission.

The following patients who discontinued due to hepatic AEs did not have a narrative included in the Appendix[12]:
HMAV 026-2613
HMBC 606-6602

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[11] All line listings requested in this document should include the trial identifier, the patient identifier, the treatment assignment, the preferred term to which the event was coded, the verbatim term for the event, and whether it was a discontinuation or an SAE (or both).

[12] HMCA 113-2302 was another patient who discontinued due to a liver-related AE. However, we note that HMCA was not included in the Overall Duloxetine Exposures Database, so we list it here just for completeness.

HMBT 106-1610
HMBT 200-2005
HMBT 302-3202

These are cases of discontinuation due to liver related AEs that we identified in looking over the abbreviated study reports for liver-related AEs. It may not be an exhaustive list of every patient who discontinued due to a liver-related AE. However, the identification of these five patients makes us concerned that other liver-related discontinuations or SAEs may have been missed. We request that you re-examine all the studies included in the "all placebo-controlled studies safety database" and the "overall duloxetine exposures database" for any liver-related SAEs and AEs leading to discontinuations to assure us that no additional cases have been misses. Please include any additional cases in the line listings requested in 3a and 3b above, as well as providing a narrative summary of the case.

5. While reviewing the liver cases, we noted that there are several occurrences of elevated CPKs.
5a. Please provide an outlier analysis for CPK using the "all placebo-controlled studies safety database" using >= 2x ULN, >=3x ULN, >=5x ULN, and >=10x ULN as the thresholds. Include only patients with normal baseline CPK in the analysis. We recognize that CPK may not have been a standard lab in all of the trials. Please include trials in which it was routinely drawn[13]. You can report the incidences for just the treatment groups PBO and ALL DLX.
5b. For the fixed dose design subset of the "all placebo controlled studies safety database", please provide the same tables as requested in 5a, but report all treatment groups (PBO, <40 DLX, 40 DLX, 60 DLX, 80 DLX, ≥120 DLX).

The following requests should NOT be limited to studies in which CPK was drawn routinely:
5c. For the "all placebo-controlled studies safety database", please provide the frequency of discontinuation due to abnormal CPK-related AEs[14] for the duloxetine and placebo groups.
5d. Please provide the list of preferred terms you use to search for abnormal CPK related AEs. They should include, but are not limited to, rhabdomyolysis, myopathy, myalgia, muscle aches, muscle cramps, increased CPK, and abnormal CPK. Because verbatim terms may be coded variably to preferred terms, the verbatim terms should also be searched using the same terms listed above to identify any additional cases that may have been coded to an unexpected preferred term.
5e. Please provide a line listing and narrative summaries for patients who discontinued due to abnormal CPK-related AEs.

6a. For the "all placebo-controlled studies safety database", please provide the frequency of abnormal CPK-related SAEs for the duloxetine and placebo groups.

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[13] Please provide a list of the studies for which CPK was routinely drawn (i.e., were included in this analysis).
[14] See 5d for a suggested approach for identifying "abnormal CPK-related" AEs.

6b. Please provide a line listing and narrative summaries for patients who had abnormal CPK-related SAEs.

7. For the "Overall Duloxetine Exposures Database", please provide the frequency of discontinuation due to abnormal CPK-related AEs and the frequency of SAEs for the duloxetine group. Please provide a line listing and narrative summaries for any patients who were not included in the line listings for 5e and 6b.

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9.3 Appendix 3: Reviewer questions sent to Lilly 6/10/04

We have briefly reviewed your response sent 6/4/04, and we have the following comments and questions:

We were concerned that the list of MedDRA terms used to search for liver-related adverse events (included below) was not adequate to identify a serious liver problem, if one had occurred.

MedDra Preferred Terms Used to Search for Liver-Related SAEs and AEs Leading to Discontinuation

MedDra Preferred Term
Hepatic enzyme increased
Hepatic function abnormal
Hepatic function abnormal NOS
Liver function test abnormal
Alanine aminotransferase increased
Aspartate aminotransferase increased
Gamma-glutamyltransferase increased
Hyperbilirubinaemia
Jaundice
Jaundice NOS
Transaminases increased

We were particularly concerned by the response to why Patient HMBT-302-3202 was not included in the 4/1/04 response. [*"Patient HMBT-302-3202 was not included in the listings for hepatic-related adverse events as the term "hepatitis" was not included as one of the hepatic search terms because hepatitis is generally used to indicate an infectious etiology"*]. From our perspective, "hepatitis" refers to any inflammation of the liver, regardless of the cause.

In this regard, we request a broader search of the adverse event database with the goal of identifying any hepatic adverse event that led to discontinuation or was categorized as a serious adverse event. We request that you search the "Overall Duloxetine Exposures Safety Database" using the MedDRA Higher Level Group Terms "Hepatic and Hepatobiliary Disorders" and "Hepatobiliary Investigations". Please provide narrative summaries for any cases identified that have not been previously submitted in the 4/1/04 or 6/4/04 submissions.

As reported by you in your response to Question 4 (p. 24, 6/4/04 submission), three patients were inadvertently left out of your 4/1/04 response because they had discontinued due to "other significant lab values". In Table 4a, there are four patients listed, presumably because your search for patients who discontinued due to "other significant lab values" identified an additional patient who discontinued for that reason. Is that presumption correct? Has the "Overall Duloxetine Exposures Safety Database" been checked to identify any patients who may have discontinued due to "other

significant lab values"? If not, please conduct that search and provide narrative summaries for any cases identified by that search.

Also, please adjust the frequency tables (Tables 6-11, 4/1/04 submission) to include those cases that were added in the 6/4/04 submission and any additional cases you identify in the above requested searches.

We would also appreciate your sending any 15 day reports for liver-related adverse events (identified using the same search terms as above) from unblinded studies that have been submitted to any duloxetine IND or NDA since the 12/22/03 submission.

As we note above, we've only had a chance to briefly review the submission that was sent on Friday June 4, 2004. As such, we may have additional queries which we will forward to you as soon as possible.

APPEARS THIS WAY
ON ORIGINAL

9.4 Appendix 4: Reviewer questions sent to Lilly 6/27/04

Questions regarding 6/3/04 submission:

1. For Tables 1a and 1b, 6/3/04 submission, in the ALKPH table, all the "n's" and corresponding "%" are "0". In essence, it appears that no patient in the placebo or treatment group had an elevation of alkaline phosphatase that exceeded 3x ULN. Is this the correct interpretation, or was there an error in the data presentation?
2. In Table 1a, the thresholds given for TBILI are 3x, 5x, and 10x ULN. Please provide the following additional thresholds for the placebo controlled study dataset and the fixed dose study dataset: >1.5x ULN; >= 2.0 mg/dl.
3. Patient 105-1503 is listed on the line listing for hepatic related SAEs (Table 3b, 6/3/04 submission), but he is not included on the line listing for discontinuations due to a hepatic-related AE, although it is clear that from the narrative that he discontinued prematurely. What was(were) the AE(s) to which his discontinuation was attributed?
4. Did patient HMAY 150-6005 have any TBILI abnormality concurrent with her transaminase elevations?
5. Did patient SBAV 120-3009 have any TBILI abnormality concurrent with her transaminase elevations?
6. SBAW 100-6000 (SBAV/SBAW 100-1002): Were the abnormal LFTs measured by the patient's insurance company ever obtained by the primary investigator? If so, what were they (please include TBILI)?
7. Did patient SBAW 114-6708 (SBAV/SBAW 114-2412) have any TBILI abnormality concurrent with her transaminase elevations?
8. The updated narrative for patient SBAY 126-3601 (submitted in a "reviewer's note" separately from the 6/3/04 submission) presents information that is inconsistent with what was previously presented. The updated narrative states that '[ ] (Visit 4), the ALT was 291 U/L, AST was 150 U/L, ALKPH was 61 U/L and GGT was 76." According to the accompanying table those were the lab values corresponding to the [ ] visit. It also says the patient discontinued the study on 14 Aug 2001, although her last dose of study drug was on 26 June 2001. Please clarify the inconsistencies in the updated narrative.
9. Did patient SAAW 029-1427 have any TBILI abnormality concurrent with her transaminase elevations?
10. Did patient E001 802-8208 have any TBILI abnormality concurrent with her transaminase elevations?
11. According to the narrative, patient 103-1309 had viral serologies that revealed a positive "A-HB-C (Igg) and anti- HC". Please define these abbreviations.
12. Please provide the TBILI values that were drawn concurrently with patient HMAU 107-1722's transaminases.
13. Did patient HMBT 200-2005 have any transaminase abnormalities associated with his hyperbilirubinemia?

14. Please provide a mean change from baseline to endpoint and maximum value by treatment group for CPK, using the "all placebo controlled studies" database.
15. Please provide a mean change from baseline to endpoint and maximum value by treatment group and dose for CPK, using the "fixed dose studies" database.

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ON ORIGINAL

9.5 Appendix 5: Reviewer questions sent to Lilly 7/1/04

Additional Questions on 6/3/04 and 6/11/04 submission:

1. In the response to Question 5d, you provide the list of search terms for abnormal CPK-related AEs. The list you provided includes "rhabdomyalysis", which is an incorrect spelling of "rhabdomyolysis". An incorrect spelling of a preferred term in a search might result in no cases of that event being detected, even if there were some. When you conducted the search of the database, did you use the correct spelling? If not, please search for that term again, using the correct spelling.
2. In the 6/10/04 data request, we requested that you adjust the frequency tables (Tables 6-11, 4/1/04 submission) to include those cases that were added in the 6/4/04 submission and any additional cases you identify in the above requested searches. Although the "updated" tables 6-11 include the one additional case identified by your search (HMBT 302-3202), they do not include the liver-related AEs that resulted in discontinuation that were coded to "other significant lab values" (listed in Table 4a, p. 26, 6/3/04 submission). Since these patients discontinued for liver-related AEs, they should be included in those tables. Please submit updated frequency tables that include these patients.

For the following questions 3-12, when you submit the requested laboratory data, please include the calendar date of each blood draw (in addition to Visit number):

3. For patient HMAY 146-5643, was there any additional CPK values drawn after one week after discontinuation (12/12/01)? If so, what were these additional CPK values?
4. For patient HMBT 206-2603, what were the CPK values that occurred during the trial (baseline and on treatment)?
5. For patient HMAU 113-2803, what were the CPK values that occurred during the trial (baseline and on treatment)?
6. For patient HMAT 019-2811, what were the CPK values that occurred during the trial (baseline and on treatment)?
7. For patient SBAU/SBAT 106-6301/106-1603, what were the CPK values that occurred during the trial (baseline and on treatment)?
8. For patient SBAW/SBAV 109-6450/109-1902, what were the CPK values that occurred during the trial (baseline and on treatment)?
9. For patient SBBM/SBAX 603-6707/603-2409, what were the CPK values that occurred during the trial (baseline and on treatment)?
10. For patient SBAW/SBAV 119-6952/119-2907, what were the CPK values that occurred during the trial (baseline and on treatment)?
11. For patient SBAX 401-1813, were there any CPK values drawn after study drug was discontinued? If so, what were they?
12. For patient SBAV 103-1305, were there any CPK values drawn between [redacted] and the start of treatment on 3/15/01? If so, what were the values? Also please provide any on-study CPK values.
13. Do the change from baseline analyses (hepatic and CPK) include only patients who had normal values at baseline, or any patient who had lab values drawn?

9.6 Appendix 6: Reviewer questions sent to Lilly 7/12/04

- HMAT 010-1922

The narrative for this patient (p. 104, 6/3/04 submission) states, "The patient was rechallenged on study drug [illegible] (Visit 7), 1 week after study drug resumed, the CPK rose again to 2658 U/L. On [illegible] the patient's CPK was 516 U/L and the patient was discontinued."

As I understand the narrative that is excerpted above, the patient remained on duloxetine after the CPK of 2658, was retested 12 days later, and the duloxetine was discontinued only after the retest was found to be 516. Is this a correct interpretation? In other words, I want to confirm that the duloxetine was not discontinued immediately after the CPK of 2658.

- In your response to Question 2 (p. 4, 7/7/04 submission), you made the following statement:

"To provide further reassurance that all discontinuations that could in some way have been related to liver-related adverse events were identified, a listing of all early discontinuations for any reason was reviewed from the overall duloxetine database. The adverse events reported at the time of discontinuation were searched for the Higher Level Group Terms "Hepatic and Hepatobiliary Disorders" and "Hepatobiliary Investigations." Patients who reported such a term but discontinued due to a reason other than "adverse event" or "other clinically significant lab values" could thus be identified."

Patient SBAM 403-4204 (narrative summary on p. 124-126, 4/1/04 submission) had a serious adverse event of "increased levels of ALT (SGPT) and AST (SGOT)". It appears that she discontinued on day 61 of therapy. Please provide the patient's reason for discontinuation, and explain why it was not identified in your broader search (as was the case for the SAE for patient HMBT 105-1503), and included in the updated tables 6a, 7a, and 10a.

- Patient SBAV 120-3009 (narrative p. 127, 4/1/04 submission) reportedly normalized her ALT and AST one week prior to drug discontinuation; however, the laboratory data you provided on p. 14, 6/30/04 submission only went through visit 5 when the elevated ALT and AST were detected. Please provide any laboratory data obtained subsequent to visit 5.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Judith Racoosin
7/15/04 02:23:15 PM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 21427
SPONSOR: Eli Lilly and Company
DRUG: Duloxetine
MATERIAL SUBMITTED: Response to second Approvable Letter
DATE SUBMITTED: December 22, 2003
REVIEWER: Roberta L. Glass, M.D.
REVIEW COMPLETION DATE: May 5, 2004

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. This is the sponsor's response to the second FDA approvable letter dated September 29, 2003. In this submission, the sponsor has included a safety update (events occurring between November 1, 1002 through October 1, 2003), world literature update, revised labeling, and study reports or summaries of all recently completed or ongoing trials (for the indications of Major Depressive Disorder, [redacted]

Duloxetine has not been marketed in other countries. [redacted]

Below is a review of the clinical material included in the current submission.

II. Data submitted

Safety Update

The cut-off date for this safety update is Oct. 1, 2003. The sponsor reports that 9 clinical studies have been completed including the following: 4 studies in patients with Major Depressive Disorder (MDD), [redacted]

Ongoing studies include 6 studies in MDD, [redacted] (Please see table 3.2 of Safety Update for details of all studies).

A review of all serious adverse events and deaths in this current submission presented a profile that was consistent with the original NDA safety data. [redacted]

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, with the exception of a high incidence of headache (n=743 or 23.1%), insomnia (n=626 or 19.4%), and dizziness (556 or 17.3%). This safety update did not include the frequency of events in the placebo group; therefore, it is unclear if these additional common events occurred with comparable frequency in the placebo group.

All cases of elevated liver function tests, and liver complications were referred to the Safety Review Team who is reviewing liver associated adverse events for the current submission.

Although occurring after the safety update cut-off, there was one case of a death by suicide reported in which a 19 year old healthy female (Patient #F1J-LC-HMCG-084-0024) hanged herself 4 days after being tapered off duloxetine in a study assessing the effects of supratherapeutic doses of duloxetine on the cardiac QTc interval. The patient's dosing ranged from 60 mg bid to 200 mg bid during the period of 1/14/04 to 2/3/04. This case is currently being investigated by FDA Division of Scientific Investigation.

Worldwide literature search

The sponsor presented a summary report of the 17 identified articles relevant to duloxetine published from November 1, 2002 to October 1, 2003. This literature summary and search was conducted by William Losin, PharmD from Lilly Research Labs. The summary concluded that there was no new safety information revealed in these publications and that the conclusions were consistent with data presented in the original NDA for duloxetine.

Regulatory Update and Foreign Labeling

According to the sponsor's submission, duloxetine has not been approved for marketing any where in the world. In an e-mail of 4/28/04, the sponsor stated that they received an approval from Mexico on 4/16/04; it is noted that Mexico was not on the sponsor's updated list of countries where duloxetine was submitted. There were no labels from other countries located in this submission.

Proposed changes to labeling

Liver Section

[Precautions Section]: The sponsor's proposed labeling attempts to separate out the discussion of liver transaminase abnormalities and liver injuries as well as use language to minimize the potential effects of the concomitant use of duloxetine and alcohol.

Comment
For detailed discussion, please refer to the safety team's review (unavailable at the time of this review). This reviewer's impression is that, at this point in the scientific understanding of liver injury, the medical community currently utilizes liver transaminase abnormalities as a signal to liver injury, and that the progression and timing to clinical symptoms is not always well understood. Therefore, it would seem logical to lump the discussion of liver injury and elevated transaminase.

It is also concerning that the sponsor's proposed language appears to minimize the effects of the concomitant use of duloxetine and alcohol as there appears to be some association of the reported cases of liver injury with the concomitant use of alcohol and duloxetine ,

Blood Pressure

In previous reviews of placebo controlled studies, duloxetine was observed to have a dose dependent increase (see review by Dr. Paul Andreason: 2/13/01; 8/16/02). The sponsor was asked to present the pooled data for the 60 mg dose in the most recent approvable letter. In response, the sponsor presented a graphic analysis of the mean change of all pooled data in the integrated database of 8454 MDD patients, and elevations at 2 and 3 consecutive visits for MDD and all patients. They reported a statistically significant difference of systolic blood pressure ($p<0.001$) for supine systolic blood pressure when measuring change from baseline to endpoint in the placebo-controlled studies, and concluded that there was no evidence of a dose dependent increase observed; however, their sample sizes used in the graphics in this submission differed from the sample sizes previously submitted in the original NDA data base (e.g. this

recent submission had smaller "n" values for the duloxetine 40 mg dose group; please refer to Table C.5.C.3 of Dr. Andreason's review of 2/13/01).

There does appear to be a dose dependent relationship for systolic blood pressure when viewing the sponsor's graphic of the % of patients with 3 consecutive visits of elevated values; but, again, the sample size is not consistent with previously reviewed material. The sponsor reports that there was no evidence of a statistically significant change from baseline for diastolic blood pressure, although there does appear to be a numerical increase from their submitted graphs.

The proposed labeling recommends [ ] It is recommended that this be reworded.

Dosing Issue

In the proposed label, the sponsor has reverted back to their preferred labeling [ ] They also mention [ ]

In an effort to support their proposal [ ] the sponsor included the study report for [ ] to relapse study followed by a continuation phase of 26 weeks [ ]. As a part of the study design, there was an optional week rescue phase open to any patient who relapsed; patients who had been taking placebo were assigned to the duloxetine [ ] dosing, and patients previously taking [ ] were assigned to a duloxetine [ ] dosing group. Therefore, the aspect of the study that looked at the dosing of duloxetine [ ] was not randomized and was open label, making it unclear if patients would have spontaneously improved on their own, and also offering no comparison group to assess efficacy.

Therefore, the sponsor still has not provided [ ] As discussed in previous reviews [ ] here is sufficient evidence supporting a [ ] day.

In conclusion, the sponsor did [ ]

Dose Related Adverse Event

The sponsor again has omitted this table [ ] In this submission (Note to the Reviewer) the sponsor includes the following table, but expresses their concern that it is uninformative (it is noted that they have omitted blood pressure as a dose related event):

[

]

Effects on Male and Female Sexual Function

Despite a request in the most recent approvable letter, the sponsor did not modify Table 2 [ ] to indicate more clearly that the numbers are percentages. It is recommended that these changes be made to this table. The sponsor has also added [ ], as this was not a primary efficacy variable, it is unclear if this is an appropriate table to include in labeling.

III. Conclusion/Recommendations

Please see the above section for recommended changes to the proposed labeling. It continues to be important to have a better understanding of duloxetine's effect on liver injury, and any increased risk with concomitant use of alcohol.

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/s/

Roberta Glass
5/5/04 08:34:06 AM
MEDICAL OFFICER

Paul Andreason
6/18/04 01:00:49 PM
MEDICAL OFFICER
See memo to file dated 6/18/2004.